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VOLUME 58  
1936

PUBLISHERS  
AMERICAN MEDICAL ASSOCIATION  
CHICAGO, ILL





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# Archives of Internal Medicine

VOLUME 58

JULY 1936

NUMBER 1

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## IDENTITY OF SPRUE, NONTROPICAL SPRUE AND CELIAC DISEASE

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The syndrome which will be discussed in this paper has acquired many names during its curious history. The term "sprue" was first used by Vincent Ketelaer<sup>1</sup> in 1669 in his description of an aphthous stomatitis occurring among the Belgians and associated with feces so copious "that several basins or pots scarcely hold these accumulations." William Hillary<sup>2</sup> is usually credited with the first description of the sprue syndrome, which he observed in the Barbados in about 1754, but the clearest modern reports were those by Manson, in China and by Van der Burch, in Java, both of which were published in 1880.

The disease soon became known as "tropical sprue," an unfortunate designation since it has contributed to the erroneous impression that sprue does not occur in temperate climates. For many years, however, sprue has been known to be endemic in North Carolina and Virginia, and from the states farther south many cases have been recorded. Snell<sup>3</sup> stated that more than a hundred cases of sprue occurring in temperate climates are on record, and one may safely presume that many more have gone unrecognized. The disease has frequently been confused with pellagra, an error which Edward Jenner Wood<sup>4</sup> clearly pointed out twenty years ago, and, from the experience of our own

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From the Departments of Medicine and Pediatrics, Duke University School of Medicine.

1 Ketelaer, Vincent, cited by Major, R. H. *Classic Descriptions of Disease*, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

2 Hillary, William, cited by Major, R. H. *Classic Descriptions of Disease*, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

3 Snell, A. M. *Clinical Observations on Nontropical Sprue*, South. M. J. **28**: 516, 1935.

4 Wood, E. J. *The Occurrence of Sprue in the United States*, *Am. J. M. Sc.* **150**: 692, 1915.

clinic we are convinced that many of the disorders that have been described as pernicious anemia with free hydrochloric acid in the gastric juice are instances of the sprue syndrome. When sprue was found to occur in temperate climates, it was termed "nontropical sprue," and more recently the term "idiopathic steatorrhea" has been coined for the syndrome, to distinguish it from pancreatic and other steatorrheas.

Gee in 1888<sup>5</sup> gave a brief but good description of a curious wasting disease of children which he termed "the coeliac disease." Heiter, working with Holt in New York, published in 1908 a small monograph entitled "Intestinal Infantilism," and Heubner, in Germany, described a condition in young children called by him "*Verdaunungsinsuffizienz*" or "chronic intestinal indigestion." It is now universally recognized that Gee, Heiter and Heubner were describing identical syndromes under different names. We agree with Thaysen<sup>6</sup> that all these names are designations for the same underlying pathologic condition occurring both in adults and in children and since the name "sprue" obviously has priority over all others, we think it best to adhere to the term "sprue" or (to broaden the conception somewhat) "the sprue syndrome." We shall present in this paper the evidence that has led us to this conclusion.

Within the past year nine patients with the sprue syndrome have come under our observation at the Duke Hospital, in two the disease began in infancy and in seven in adult life; none of the patients has ever resided in the tropics. Since space is not available for the presentation of all the histories, only two will be given in detail, one (case 3 fig. 1) is a typical example of sprue in an adult and the second (case 5 fig. 2) is an instance of sprue which, beginning in infancy, has persisted to the age of 17, causing dwarfism. A brief synopsis of the other seven cases is given.

#### REPORT OF CASES

CASE 1—A. B., a woman aged 44, the wife of a farmer residing in North Carolina, who had never lived out of the state, complained of indigestion, weakness and great loss of weight (she had lost 85 pounds [38.6 Kg.] or 50 per cent of her former weight).

Examination of the blood showed macrocytic hyperchromic anemia. The stools were not analyzed for fats. Analysis of the gastric content showed no free hydrochloric acid during fasting and 68 degrees hydrochloric acid after stimulation with alcohol and histamine. (These results were confirmed by a second analysis.) A test for dextrose tolerance showed a very flat curve, the maximum rise in the sugar content of the blood being 11 mg. per hundred cubic centimeters.

Marked and steady improvement resulted from a diet rich in proteins with the addition of liver.

<sup>5</sup> Gee, Samuel. On the Coeliac Affection, St. Barth. Hosp. Rep. **24** 17 1888.

<sup>6</sup> Thaysen, T. E. II. (a) Nontropical Sprue. A Study in Idiopathic Steatorrhea, Copenhagen, Levin & Munksgaard, 1932, (b) La steatorrhée idiopathique, la sprue tropicale et non tropicale et l'infantilisme intestinal, Arch. d. mal. de l'app. digestif **24** 123, 1934.

CASE 2—M R, a widow aged 60, had always lived on a farm in North Carolina. She complained of diarrhea of four years' duration and of weakness and loss of weight (she had lost 50 pounds [22.7 Kg], or 40 per cent of her former weight).

Examination of the blood showed macrocytic hyperchromic anemia. The stools were bulky, frothy, unformed and fatty. Analysis of the gastric content showed no free hydrochloric acid during fasting and 36 degrees free hydrochloride acid after stimulation with alcohol and histamine. A test for dextrose tolerance showed a very flat curve, the maximum rise in the sugar content of the blood being 9 mg per hundred cubic centimeters. There was generalized osteoporosis, the calcium content being 7.4 mg and the phosphorus content 2.4 mg per hundred cubic centimeters of blood.

Under liver therapy the patient gained 26 pounds (11.8 Kg), or 36 per cent of her weight at entrance, in five months.

CASE 3—J M T, a man aged 51, was admitted to the Duke Hospital on April 4, 1935, complaining of diarrhea of eighteen months' duration and great loss of weight and strength (he had lost 58 pounds [26.3 Kg], or 37 per cent of his former weight).

The family and the past history were noncontributory.

*Present Illness*—Fifteen years before, while the patient was working as the foreman of a construction gang in Louisiana, indigestion developed. The patient stated that about one-half hour after meals he began to suffer from pain in the abdomen, this was of a burning character and accompanied by eructations of gas. He had what he described as an "acid taste" in his mouth and began to have periods of diarrhea alternating with periods of constipation. The diarrhea recurred each spring and was characterized by the passage of large amounts of foul-smelling semiliquid stools without blood or mucus. He had periods of abdominal pain, especially early in the morning, which were relieved by a bowel movement. During the periods of diarrhea he lost considerable weight, but he regained it after the diarrhea had ceased. His color gradually became sallow and yellowish. His diet was composed largely of carbohydrates.

Five years before his admission to the hospital the patient returned to his home in North Carolina. He improved, and his health remained fairly good until eighteen months before admission, when the diarrhea recurred with great severity, the number of stools varying from two to ten daily. He became so weak and lost so much weight that he was no longer able to work. He suffered almost continuously from gaseous intestinal indigestion associated with the passage of enormous frothy, foul stools. During the past year his mouth had been sore and "scalded." His diet had consisted largely of milk and eggs, fruit juices, bananas and a little liver. He had grown so weak in the past few months that he had been forced to keep to his bed and had walked only with assistance. He had noticed progressive numbness of his hands and feet. He stated that when the feet were "asleep" he could not tell their position in the bed. His maximum weight was 155 pounds (70.3 Kg), and when he entered the hospital he weighed 97 pounds (44 Kg).

*Examination* (fig 1)—The positive findings were as follows. The patient was emaciated to the "skin and bones" stage. He weighed 97 pounds (44 Kg) and was about 5½ feet (164 cm) in height. The skin was grapefruit colored, the tongue was red and beefy and showed marked papillary atrophy. Except for these findings the general physical examination gave negative results.

Neurologic examination revealed diminution of the ankle and knee jerks and a distinct lowering of vibratory sensation over the feet, but no other abnormalities.



The blood showed typical hyperchromic macrocytic anemia with anisocytosis and poikilocytosis. The hemoglobin content was 64 Gm (41 per cent of 155 Gm), the red blood cells numbered 1,650,000, the color index was 1.24, the mean corpuscular volume, 120 cubic microns, the mean corpuscular hemoglobin content, 38.7 per cent, the percentage of reticulocytes, 1 per cent, the white blood cell count, 3,900. The differential count gave normal results. The Wassermann test was negative. The calcium content of the serum was 7.6 mg per hundred cubic centimeters, the albumin content, 2.89 Gm, and the globulin content, 1.87 Gm. The phosphorus content of the blood was 3.2 mg per hundred cubic centimeters,

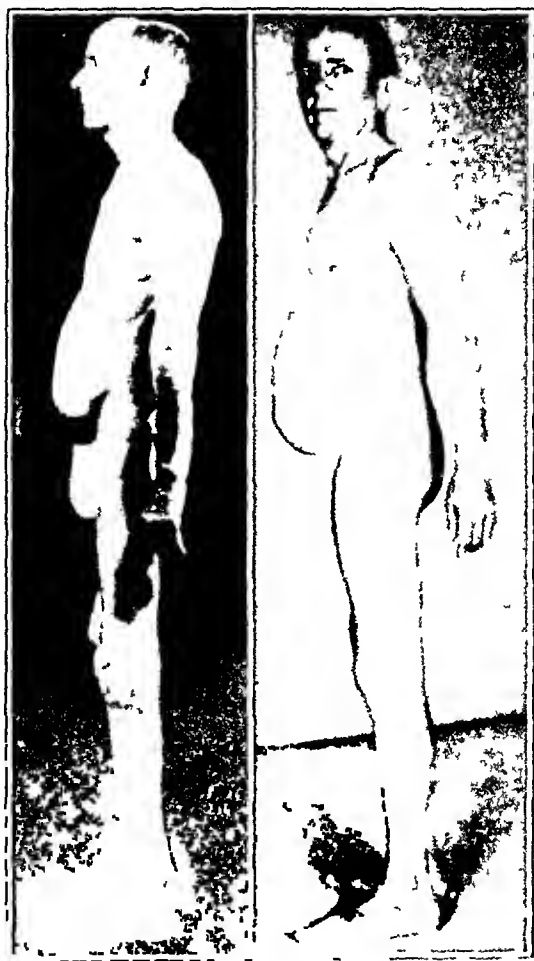


Fig. 1 (case 3)—Photographs of the patient, illustrating the effect of treatment with liver after the patient gained 15 pounds (6.8 kg) in thirty days and after he had received liver extract for six months.

and the cholesterol content, 150 mg. Analysis of the gastric content showed no free hydrochloric acid in the stomach during fasting, but forty-five minutes after stimulation with histamine there was observed to be 4 degrees. The basal metabolic rate was -15 per cent. Oral administration of 100 Gm of dextrose gave a flat curve, the sugar content of the blood being 83 mg per hundred cubic centimeters during fasting and 87 mg one-half hour, 95 mg one hour, 94 mg two hours, and 88 mg three hours after administration of dextrose. After intravenous administration of 25 Gm of dextrose the sugar content of the blood was as follows: during fasting, 77 mg per hundred cubic centimeters; one-half hour after

injection, 145 mg, one hour after injection, 103 mg, two hours after injection 78 mg, and three hours after injection, 77 mg. The van den Bergh test gave an indirect reaction. The bilirubin content of the serum was 0.8 mg per hundred cubic centimeters. The icteric index was 15. Studies of the bones showed no decalcification. Roentgen examination of the gastro-intestinal tract showed no defects of the stomach or small intestines, as described by Mackie and by Snell, but marked dilatation and sluggishness of the colon were observed.

The stools were constantly large, frothy, and ill smelling, their number varying from two to eight in twenty-four hours. Examination of a twenty-four hour specimen of April 8, 1935, gave the following results: total dry matter, 7.95 per cent of the total weight (normal value, 20 per cent), total fat 38.6 Gm, or 29 per cent of the dry matter (normal value, 17.5 per cent), free fatty acid, 28.5 Gm, or 21.4 per cent of the dry matter (normal value, 5.5 per cent), neutral fat, 6.9 Gm, or 5.2 per cent of the dry matter (normal value, 7.3 per cent), soap, 3.2 Gm, or 2.4 per cent of the dry matter (normal value, 4.6 per cent), total nitrogen, 4.6 Gm, or 3.4 per cent.

It was decided to try the therapeutic value of addisin, made after the method of Morris from the patient's own gastric juice and from the gastric juice of normal persons. In neither experiment was there any rise of the reticulocyte count worthy of note.

*Course*—Six weeks after admission the patient's condition was unchanged or slightly worse. Sternal puncture revealed hypertrophic bone marrow with tremendous numbers of erythroblasts and myeloblasts. There were 25 per cent reticulated red blood cells. The picture presented by the peripheral blood had not altered, and the number of reticulocytes, which were counted daily, had never been above 2 per cent.

Liver extract was then given by mouth. This was done in order to compare the results with those produced by the ingestion of the extract in pellagra, as Dr. Smith and Dr. Ruffin of the clinic of the Duke Hospital had found this extract inefficacious in controlling the symptoms of the disease when administered orally. The patient received 120 cc of the extract by mouth for five days.<sup>7</sup> Five days after this treatment was begun the reticulocyte count had risen from 0.5 to 5 per cent, eight days later it reached a maximum of 10.8 per cent, and then it gradually declined, reaching 0.1 per cent on the fourteenth day. The number of red cells, however, showed only a slight rise, the count being 1,780,000. Nevertheless, within forty-eight hours after liver extract was given the patient's general condition showed an extraordinary change for the better. His appetite became ravenous, whereas during the preceding six weeks he scarcely ate at all. He had lain in a condition of hebetude and exhaustion, sleeping much of the time, but after liver extract was administered his manner changed gradually to moderate alertness. The transformation would have been incredible had one not witnessed so often the same type of change in patients with pernicious anemia. He became very constipated, whereas before treatment he had had diarrhea and had passed frequent large, frothy, ill-smelling stools. The tongue became normal in appearance.

Twenty-nine days before the patient was discharged intramuscular administration of concentrated liver extract was begun in doses of 5 cc, twenty-three injections were given. The patient received in addition 30 cc daily of a crude whole liver extract by mouth and also as much liver as he could eat. His diet was otherwise unchanged from the regular ward diet, no attempt was made to exclude or emphasize any one type of foodstuff except that the patient was encouraged to

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7 The liver extract was supplied by Ely Lilly & Company, Indianapolis

eat six bananas daily. On this regimen he ate ravenously and gained 17 pounds (7.7 Kg) in three weeks. He became jovial and said that he had not felt so well for fifteen years.

On the day of discharge an examination of the blood showed red cells, 2,900,000, hemoglobin content, 9.8 Gm (63 per cent of 15.5 Gm) color index, slightly over 1, white cells, 6,200, reticulocytes, 1 per cent. The size and shape of the erythrocytes were normal, being in striking contrast to the anisocytosis and poikilocytosis seen on entry. A final gastro-intestinal roentgen study, made two days before discharge, showed nothing abnormal, except that the colon which was formerly "sluggish and dilated" now showed hypermotility. During the last month in the hospital the patient was constipated, as a rule, but he had two episodes of loose, frequent stools.

*Follow-Up Note*—The patient was seen again on Oct. 26, 1935, at which time he had gained a total of 69 pounds (31.3 Kg) since his admission to the hospital on April 3, 1935 (a gain of 70 per cent of his weight on admission). The red blood cell count was 4,710,000, the hemoglobin content, 14.3 Gm (92 per cent), and the color index, 0.98. The patient looked the picture of health and stated that he felt "as well as ever." His only complaint was of a rare recurrence of diarrhea which lasted for only a few hours.

**CASE 4**—M. M., a girl aged 27 months failed to gain weight and passed bulky frothy, fatty stools. Examination of the blood showed macrocytic hyperchromic anemia. The red cell count was 1,700,000, the hemoglobin content, 7.8 Gm (50 per cent), the color index, 1.44 and the mean corpuscular volume, 147. Analysis of the gastric content showed 50 degrees of free hydrochloric acid during fasting. A test for dextrose tolerance demonstrated a flat curve the maximum rise in the sugar content of the blood being 37 mg. per hundred cubic centimeters.

Marked improvement in every way resulted from a diet rich in proteins and vitamins, to which liver was added.

**CASE 5**—I. McC., a youth aged 17, was admitted to the medical service of the Duke Hospital on June 16, 1935. He had been studied on a former admission when he was 11 years old in the pediatric department.

The family history was not important.

*Past History*—When the patient was 18 months old he had a severe attack of dysentery, and the mother noticed that the abdomen began to enlarge. For the next two years he was weak, he walked with difficulty, and the abdomen gradually increased in size. During all this time his bowels had been loose—he had from four to eight stools daily—and severe hemorrhoids had developed. When the patient was 3 years old he was given a daily diet of one egg, eight bananas, a tablespoonful of jello, cottage cheese, cereals and four glasses of lactic acid milk. On this diet he improved for a while, but in a few months symmetrical cutaneous lesions developed, which were diagnosed as pellagra. Yeast was added to his diet together with liver, cod liver oil and fruit juices, the cutaneous lesions disappeared and considerable improvement in his general condition occurred. However, for the next eight years he failed to grow normally, and the diarrhea persisted, large foul stools being passed.

When the patient was 11 years of age the following diagnoses were made: celiac disease with dwarfism, secondary anemia and subsiding pellagra. It is of interest that when the patient was seen two months after discharge his anemia which had been of a secondary type, had changed to a hyperchromic type. The red blood cells numbered 1,900,000, the hemoglobin content was 46 per cent and the color index, 1.2.

*Present Illness*—On June 19, 1935, the patient became acutely ill with fever and sharp pains in the lower portion of the abdomen. The stools became more frequent. On June 14 he experienced difficulty in voiding, and his bladder became swollen and painful. The next day he became edematous, the legs swelling first and then the body, face and arms, but this had subsided at the time of entrance.

*Examination*—The patient, although 17 years of age, had the physical development of a boy of 7 years (fig 2), being about 4 feet (120 cm) tall and weighing 50 pounds (22.7 Kg). The skin was dry, coarse and wrinkled, there was little subcutaneous fat, but the abdomen was huge and protuberant. The voice was high pitched and childish. The genitalia were infantile. The results of physical and neurologic examinations were otherwise normal.



Fig 2 (case 5)—Photograph of the patient, showing dwarfism due to sprue. The patient's height was about 4 feet (120 cm), his weight, 50 pounds (22.7 Kg).

The blood count revealed a secondary anemia, the red cell count being 2,730,000, the color index 0.78 and the white cell count 12,000. The differential count was normal. The Wassermann test was negative. A dextrose tolerance test, 30 Gm of dextrose being administered orally, gave a flat curve, the sugar content of the blood being as follows: during fasting, 83 mg per hundred cubic centimeters, one-half hour after administration of dextrose, 92 mg, one hour after administration, 85 mg, two hours after administration, 86 mg, and three hours after admin-

istration, 75 mg. The cholesterol content was 136 mg., the calcium content, 81 mg., and the phosphorus content, 44 mg., per hundred cubic centimeters of blood. The plasma proteins totaled 6.2 Gm. per hundred cubic centimeters—2.9 Gm. of albumin and 3.3 Gm. of globulin, a ratio of 47:53.

The stools were tan, voluminous, foamy and liquid for the most part and had a very foul odor. No parasites were found. There was no evidence of undigested food except for a moderate excess of fat, as revealed by staining with sudan III. Tests with benzidine and guaiac were negative. Chemical analysis of a twenty-four hour specimen of stool gave the following results: total dry matter, 39 Gm.; total fat, 44.2 Gm.; free fatty acid, 26.1 Gm.; neutral fat, 13.1 Gm.; soaps, 4.9 Gm.; and nitrogen, 7.7 Gm.

Analysis of the gastric content was made. During fasting there was no free hydrochloric acid; the total acid was 6 degrees of tenth-normal sodium hydroxide. Forty-five minutes after stimulation with 0.008 Gm. of histamine the free hydrochloric acid was 50 degrees and the total acid, 80 degrees.

The basal metabolic rate was +20.

Röntgen studies of the colon after administration of barium sulfate showed many redundant loops and elongation. The findings were consistent with megacolon. Röntgenograms of the skeleton showed delayed epiphyseal development.

*Diagnosis*—The case was regarded as an example of classic infantilism resulting from sprue. Administration of large quantities of liver together with calcium, cholesterol, iron and a high vitamin diet was prescribed which produced marked improvement in his condition.

**CASE 6**—**I**, a married woman aged 29, had lived on a farm in North Carolina all her life. She complained of diarrhea, weakness and great loss of weight (she had lost 40 pounds [18.1 Kg.] or 39 per cent. of her former weight).

Examination of the blood showed macrocytic hyperchromic anemia. Analysis of the stools gave the following results: total fats, 37.7 per cent.; free fatty acids, 20 per cent.; neutral fat, 6 per cent.; soaps, 11.9 per cent. Analysis of the gastric content showed 5 degrees of free hydrochloric acid during fasting and 16 degrees after stimulation with histamine. A test for dextrose tolerance showed a very flat curve; the maximum rise in the sugar content of the blood being 4 mg. per hundred cubic centimeters of blood.

There was marked response to liver therapy; the patient gained 60 pounds (27.2 Kg.) in weight in sixty-six days.

**CASE 7**—**II**, a married woman aged 25, who had lived on a farm in North Carolina all her life, complained of diarrhea which had been present for three and one-half months. She had given birth to a child eight months before she was seen. She showed evidence of deficient nutrition.

Examination of the blood disclosed macrocytic hyperchromic anemia. The stools were copious and watery; their composition was as follows: total fats, 46.4 per cent.; free fatty acids, 25.5 per cent.; neutral fat, 17.4 per cent.; soaps, 3.4 per cent.; and total nitrogen, 3.3 Gm. Analysis of the gastric content disclosed no free hydrochloric acid either during fasting or after stimulation with histamine. The test for dextrose tolerance showed a flat curve; the maximum rise in the sugar content of the blood being 12 mg. per hundred cubic centimeters.

Prompt and sustained improvement resulted from adequate liver therapy.

**CASE 8**—**K**, a girl aged 14, who had lived in North Carolina all her life, had suffered from chronic diarrhea for the past six years. The stools were greasy and bulky. Examination of the blood showed slight hypochromic anemia; there were 4,300,000 red cells and 82 per cent. hemoglobin. Analysis

of the stools gave the following results total fat 52.7 per cent free fatty acids, 23.8 per cent, neutral fats, 12.9 per cent, soaps, 1.6 per cent, total nitrogen, 4.3 Gm. Analysis of the gastric content showed 30 degrees free hydrochloric acid during fasting and 21 degrees after stimulation with histamine. The tests for dextrose tolerance showed a flat curve, the maximum rise in the sugar content of the blood being 13 mg. per hundred cubic centimeters.

At the time of writing the patient was receiving treatment with liver extract. Marked improvement was evident.

CASE 9—B. C., a married man aged 30, who had lived on a farm in North Carolina all his life complained of diarrhea, weakness and loss of weight which began two and one half years before he was seen. Examination of the blood showed macrocytic hyperchromic anemia. Analysis of the stools gave the following results total fat, 43.1 per cent, free fatty acid, 11.2 per cent, neutral fat, 8.1 per cent, soap, 23.8 per cent, total nitrogen, 12.9 Gm. Analysis of the gastric content showed no free hydrochloric acid during fasting and 37 degrees free hydrochloric acid after stimulation with histamine. The test for dextrose tolerance showed a flat curve, the maximum rise in the sugar content of the blood being 23 mg. per hundred cubic centimeters.

At the time of writing the patient shows marked improvement as the result of liver therapy.

*Summary*—In the nine instances of the sprue syndrome reported here, the patients' age varied from 27 months to 60 years. Eight of nine patients showed macrocytic hyperchromic anemia, eight showed marked steatorrhea (the stools of A. B. [case 1] were not chemically analyzed), eight of nine patients had free hydrochloric acid in the gastric secretions after stimulation with histamine, all nine showed very low curves for the sugar content of the blood after the ingestion of 1.5 Gm. of dextrose per kilogram of body weight. The therapeutic response to liver extracts was prompt and marked in the nine patients.

The fundamentally identical findings in the nine cases which we have carefully studied, together with a review of the literature, have led us to agree fully with Thaysen<sup>6</sup> that celiac disease and sprue represent the childhood and the adult phase of the same underlying disease. The clinical picture of infantile sprue, with or without rickets, seems at first to have little in common with the picture of sprue in the adult. Infantile sprue and adult sprue, however, bear the same relationship to each other as do cretinism and myxedema. We shall consider now in more detail the separate elements of the sprue syndrome.

#### ETIOLOGY

There are certain features of celiac disease and sprue which point definitely to a deficiency state, however produced, as at least a factor in the production of the syndrome. The occurrence of osteoporosis and tetany in the child and of osteomalacia and tetany in the adult, associated in both with a low calcium and phosphorus content of the blood

macrocytic hyperchromic anemia, xerophthalmia and night blindness,<sup>8</sup> mental changes, aphthous stomatitis and enteritis—these are changes recognizably due to deficiencies of accessory food factors. The gastro-intestinal mucosa is a highly specialized organ, resistant to infection and possessing great powers of regeneration. We believe that a deficiency of one or more accessory food factors lowers these powers of resistance and regeneration, leading to severe alterations of the functions of the gastro-intestinal mucosa. Eventually the uncorrected deficiency leads to a state of atrophy and dysfunction of the whole intestine. It is highly probable that, as in other deficiency states, cells of the whole body suffer. On the other hand the condition is functional and amenable to treatment.

#### AGE AND MODE OF ONSET

Samuel Gee<sup>9</sup> of St. Bartholomew's Hospital published in 1888 a brief article entitled "On the Coeliac Affection," which deserves to be included among the minor medical classics. Phrased in a quaint staccato style and written with the utmost brevity, his description has been but slightly amplified by subsequent observers. We quote from the opening paragraph: "There is a kind of chronic indigestion which is met with in persons of all ages, yet is especially apt to affect children between one and five years old." In support of Gee's assertion that the coeliac disease "is met with in persons of all ages" we quote from Bailey Ashford's<sup>10</sup> article on sprue:

In a smaller number of cases . . . sprue starts as a dysentery or as a more or less violent gastro-entero-colitis with vomiting, fever, tenesmus and small mucous, often bloody stools. This mode of beginning is especially frequent among young children from two to five years of age.

Ashford found eighty-seven patients under 10 years of age among seven hundred and twenty patients with sprue in Puerto Rico. Miller<sup>10</sup> gave an excellent description of sprue occurring in a boy of 11 and Bennett, Hunter and Vaughan<sup>11</sup> have reported the occurrence of the sprue syndrome in patients aged 3½, 10, 11, 13 and 52 years. Weiss and his co-workers<sup>12</sup> among eighty-five patients with "tropical sprue" found five who were under 5 years of age.

8 Riddell, W. J. B. Coeliac Disease Associated with Night Blindness and Xerosis Conjunctivae, *Tr. Ophth. Soc. U. Kingdom* **53** 295, 1933.

9 Ashford, Bailey, in Christian, Henry A., and Mackenzie, J. *Oxford Medicine*, New York, Oxford University Press, 1921, vol. 5, chap. 27, p. 640.

10 Miller, R. Sprue Commencing at the Age of Eleven and One-Half Years. *Tr. Roy. Soc. Trop. Med. & Hyg.* **27** 413, 1934.

11 Bennett, T. I., Hunter, D., and Vaughan, J. M. Idiopathic Steatorrhea (Gee's Disease), *Quart. J. Med.* **1** 603, 1932.

12 Weiss, C., Landron, F., Costa-Mandry, O., and Weiss, D. W. Summary of Investigations on the Etiology of Tropical Sprue in Porto Rico. *Ann. Int. Med.* **2** 1198 (May) 1929.

The onset of infantile sprue, or celiac disease occurs most often between 1 and 2 years of age. Symptoms frequently had been present for several months before the parents sought medical advice, so insidious is the malady. In the early stages the patient loses his appetite, begins to lose weight, becomes cross and irritable and suffers from periods of moderate fatty diarrhea associated with vomiting. The progressive loss of weight, the weakness and the diarrhea finally bring him under medical observation.

Adult sprue and so-called nontropical sprue present similar symptoms, though the patient, being older, becomes aware earlier in the disease of subjective symptoms which the infant cannot voice except by petulance and irritability. There is a sense of fullness after eating due to gas in both the stomach and the intestine, accompanied by recurring diarrhea varying greatly in severity and later by soreness of the tongue and stomatitis. Diarrhea is not a constant feature, the patient may pass but one large fatty, ill smelling stool daily. The tendency is for the progress to be gradual, and the disease may be of very mild degree, showing exacerbations and remissions for years. Great loss of weight, nervousness, malaise and extreme fatty diarrhea are characteristics of the fully developed picture. A patient may lose as much as 50 per cent of his body weight, and rapid increase of weight often occurs as a result of proper treatment both in patients with celiac disease and in those with sprue.

#### PATHOLOGY

Neither sprue nor celiac disease presents a definite and constant pathologic picture. Hess and Saphir<sup>13</sup> have demonstrated by special staining methods a fibrosis of the pancreas with small cell infiltration, but there is no evidence that pancreatic deficiency exists in sprue. The changes in the intestines are those of chronic inflammation and edema possibly the result of secondary infection, and atrophy of the whole intestine. The other organs show simply the effects of chronic malnutrition. The great depletion of the panniculus adiposus, common to both syndromes, is the most striking pathologic change. The absence of pathologic changes at autopsy strongly supports the theory that a disorder of metabolism, or a deficiency state, is a probable etiologic factor, and the studies of Miller and Rhoads<sup>14</sup> on the production of a chronic deficiency state in swine corroborate this opinion.

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13 Hess, J. H., and Saphir, O. Celiac Disease (Chronic Intestinal Indigestion), *J. Pediat.* **6** 1, 1935.

14 Miller, D. K., and Rhoads, C. P. The Experimental Production of Loss of Hematopoietic Elements of the Gastric Secretion and of the Liver in Swine with Achlorhydria and Anemia, *J. Clin. Investigation* **14** 153, 1935.



## STOOLS

We quote again from Gee

Signs of the disease are yielded by the faeces being loose, not formed, but not watery, more bulky than the food taken would seem to account for, pale in color, as if devoid of bile, yeasty, frothy, an appearance probably due to fermentation stinking, stench often very great, the food having undergone putrefaction rather than concoction

This is an excellent description of the stools in cases of advanced sprue, though in the beginning the diarrhea is watery, and indeed in the mild form diarrhea may not be present

The stools both of patients with sprue and of those with celiac disease contain an excess of fat, the fat content being about three times greater than normal but it is generally agreed that the fat-splitting function is normal in contrast to the condition existing in steatorrhea due to pancreatic deficiency. It has been shown<sup>15</sup> that the feces contain more fat than is present in the diet thus indicating an excess excretion of fat through the intestinal epithelium. The low values for the calcium content of the blood frequently encountered in sprue and celiac disease are probably due to vitamin D deficiency and inadequate acidity of the intestinal contents leading to poor absorption of calcium.<sup>16</sup> The values for calcium and phosphorus in the blood are frequently low both in sprue and in celiac disease. The percentage of nitrogen in the feces does not as a rule vary significantly from the normal. The stools are pale thin and often frothy and fermented in appearance and their bulkiness is out of all proportion to the intake of food. Remissions and exacerbations of the diarrhea are common and constiveness may alternate with frequency.

Light of the nine patients with the sprue syndrome observed by us had free hydrochloric acid in the gastric juice after stimulation with histamine, this is the almost universal rule both in children<sup>17</sup> and in adults the observations contrasting sharply in this respect with those on patients with pernicious anemia.

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The anemia of sprue is typically first hypochromic and later becomes hyperchromic and macrocytic. There are, however, exceptions to this rule. The typical anemia of celiac disease, or infantile sprue is hypochromic and only rarely becomes hyperchromic and macrocytic. This difference in the behavior of the bone marrow in the two syndromes

15 Bauer, E. L. Celiac Disease, *Am J Dis Child* **35** 414 (March) 1928

16 Macrae, O., and Morris, N. Metabolism Studies in Celiac Disease, *Arch Dis Childhood* **6** 75, 1931

17 Ogilvie, J. W. Gastric Secretion in Celiac Disease, *Arch Dis Childhood* **10** 93, 1935

has been urged by Parsons<sup>18</sup> as an argument for the separation of the two conditions. The point becomes less impressive when closely examined. The bone marrow of children reacts rarely in a hyperchromic, macrocytic fashion. So true is this that the very existence of pernicious anemia in childhood is a question of doubt. In the celiac syndrome then, one can say only that the normal hypochromic reaction to injuries of the bone marrow in childhood obtains and that the underlying causes of the disease rarely<sup>11</sup> produce a reversal of this normal reaction. The condition is quite different in adults. In them the bone marrow frequently shows a hyperchromic, macrocytic reaction to diverse injuries (deficiency states, cancer, injuries to the liver, infestation with *Dibothriocephalus latus*, pregnancy, etc.). That it so reacts in patients with sprue, which is due in part at least, to a deficiency state, is not surprising and certainly offers no defensible criterion for the separation of the syndromes of sprue and celiac disease. When improvement occurs, the blood picture of sprue loses its hyperchromic macrocytic character and becomes hypochromic or normal.

#### BLOOD SUGAR CURVES

Low curves for sugar content of the blood (after the ingestion of 1.5 Gm. of dextrose per kilogram of body weight) have been found with greater than normal frequency in cases of "tropical" sprue, of "nontropical" sprue and of celiac disease. Thaysen<sup>17</sup> regarded a rise of less than 40 mg. per hundred cubic centimeters as a low curve and stated that it has been found in only 5 per cent of normal persons. He observed persistently low curves in four of eight cases of "nontropical" sprue, in one of two cases of "tropical" sprue and in the one case of celiac disease which he studied. While the curves tend to be low, the rise is also prolonged over a period of two hours or more. Svensgaard<sup>19</sup> observed similar curves in two cases of celiac disease. She also observed marked rises in the sugar content of the blood when epinephrine was given in addition to 1.5 mg. of dextrose per kilogram of body weight. McLean and Sullivan<sup>20</sup> showed that the curve was low in fourteen children with celiac disease and that no tendency of the curve to rise after the ingestion of 1.75 Gm. of dextrose per kilogram of body weight was observed.

We believe that this constant low blood sugar curve is one of the most helpful differential findings in the sprue syndrome. In all our cases the curve was very low after the ingestion of 1.5 Gm. of dextrose

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18 Parsons, L. G. Celiac Disease, *Am J Dis Child* **43** 1293 (May, pt 2) 1932.

19 Svensgaard, E. Blood Sugar in Intestinal Infantilism. *Acta pædiat* **9** 22, 1929.

20 McLean, A. B., and Sullivan, R. C. Carbohydrate Tolerance in Infants and Young Children with Celiac Disease, *Am J Dis Child* **38** 16 (July) 1929.

per kilogram of body weight (fig. 3). On the other hand, the intravenous injection of dextrose results in a prompt increase in the sugar content of the blood, though the curve rises to slightly lower levels than normal. The curve tends to return to normal levels as the patient recovers. Of eight cases of pancreatic steatorrhea Thaysen<sup>18</sup> found that in seven there was a diabetic type of curve and in one a normal curve.

#### CENTRAL NERVOUS SYSTEM

The mournful querulous pessimistic faces of a patient with celiac disease mirror the child's mental state. Such a child is "difficult", nothing pleases him, and he is exceedingly irritable and emotional. Sleep is broken and disturbed; the child frequently crying out and moving restlessly.

The sufferer from adult sprue exhibits the counterpart of the nervous symptoms seen in the child. Such a patient is often emotionally unstable and depressed—exhibiting a strong leaning to pessimism—irritable, forgetful and filled with vague aches and pains. He is headstrong and even when reduced to skin and bones insists on dragging himself about (Ashford). Insomnia is troublesome. Subacute combined degeneration of the spinal cord is said not to occur in sprue but this is incorrect, as it unquestionably does occur occasionally.<sup>19</sup> Paresthesia of the hands and feet is a common complaint.

#### RICKETS AND OSTEOPOROSIS

The changes in the bones in chronic steatorrhea due to various causes are most interesting. The principal change in sprue-celiac disease is osteoporosis. In infantile sprue, owing to the earlier age incidence, rickets is occasionally found. These changes in the bones are a result of the excessive excretion of calcium in the stools in the form of calcium soaps as well as of lack of absorption of vitamin D and of calcium.

McCrudden and Fales<sup>20</sup> first noted osteoporosis in celiac disease, associated with a negative calcium balance and an inadequate retention of phosphorus. Since then osteoporosis has often been observed and is the rule when the involvement is severe. Parsons in 1913 first demonstrated a case of celiac disease associated with definite rickets. There has been much controversy as to the type of rickets. Hess<sup>21</sup> stated

From the standpoint of rickets, the lesions in the bones which accompany celiac disease must be regarded as being the result of a deficiency in calcium.

21 Weir, J. F., and Adams, M. Idiopathic Steatorrhea (Nontropical Sprue) Metabolic Studies During Treatment, Report of a Case, *Proc. Staff Meet. Mayo Clin.* 9:743, 1934.

22 McCrudden, F. H., and Fales, F. L. Complete Balance Studies of Nitrogen, Sulphur, Phosphorus, Calcium and Magnesium in Intestinal Infantilism, *J. Exper. Med.* 15:450, 1912.

23 Hess, A. Rickets, Osteomalacia and Tetany, Philadelphia, Lea & Febiger 1929.

On the other hand, Parsons considered the osteoporotic bones of patients with celiac disease to be potentially rachitic and he at times found low values for phosphorus. Fanconi found the values for phosphorus to be low in fifteen cases of "celiac rickets." The changes in the bone are considered by Parsons to pass through three distinct phases (1) the usual type of infantile rickets (low values for phosphorus), (2) healing with arrested growth and subsequent osteoporosis and (3) late development of rickets associated with low values for calcium and sometimes for phosphorus in the blood. Late development of rickets occurs only if the disease is severe and of long standing. Parsons' youngest patient with "celiac rickets" was 5 years of age.

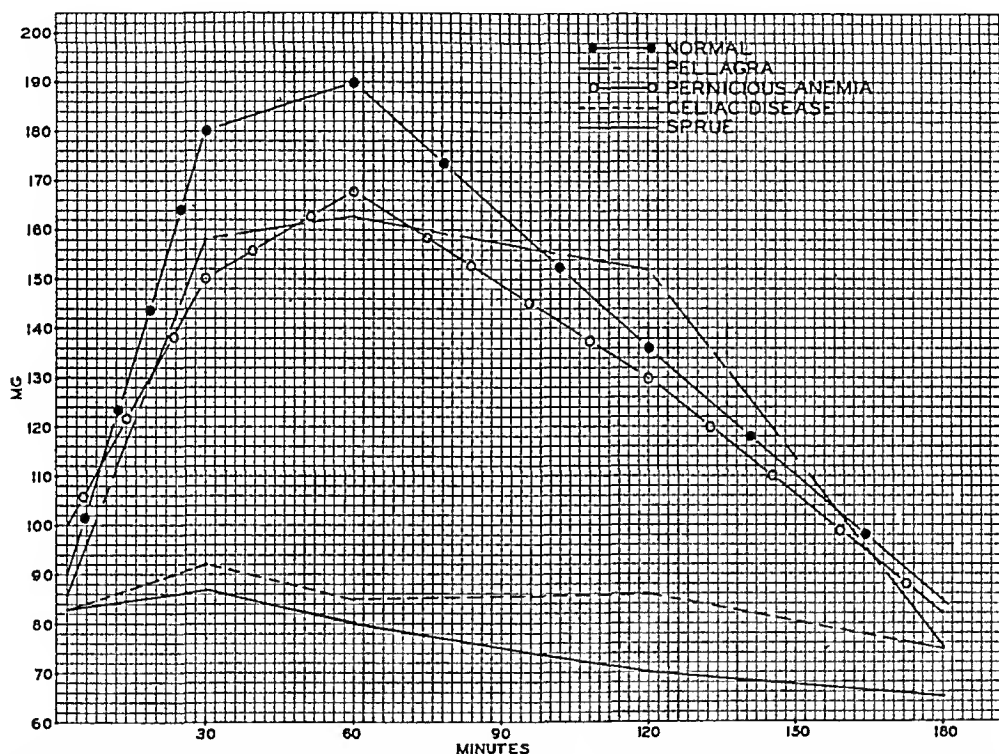


Fig 3—Curves showing the sugar content of the blood after ingestion of 1.5 Gm of dextrose per kilogram of body weight

Bennett, Hunter and Vaughan<sup>11</sup> found varying degrees of osteoporosis in twelve of fifteen patients with "idiopathic steatorrhea." Holmes and Starr<sup>24</sup> and Engel<sup>25</sup> each reported a case of "tropical" sprue with osteoporosis, but otherwise its presence or absence has seldom been mentioned. In the second and fourth cases of our series there was marked osteoporosis. Thaysen, in reviewing the literature on "non-

<sup>24</sup> Holmes, W. H., and Starr, P. A Nutritional Disturbance in Adults Resembling Celiac Disease and Sprue, *J A M A* **92** 975 (March 23) 1929

<sup>25</sup> Engel, A. A Case of So-Called Sprue, *Acta med Scandinav* **75** 341, 1931

tropical' sprue, found that seven of thirty-four patients had osteoporosis. Five of the seven also had active tetany. In tropical regions sprue seldom causes a marked lowering of the calcium content of the blood. This may be explained by the abundance of ultraviolet rays and their power to synthesize vitamin D from the inactive ergosterol of the skin. Fairley<sup>26</sup> in three cases of "tropical" sprue, however, found calcium concentration of less than 64 mg per hundred cubic centimeters of blood. The inorganic phosphorus content of the blood in "nontropical" sprue was found by Scherer<sup>27</sup> in one case to be 2.41 and 2.27 mg per hundred cubic centimeters while Meyer's<sup>28</sup> patient had 2.02 mg. Both of these patients had tetany. In cases of celiac disease low values for phosphorus and calcium have often been found and tetany is common.

Whether one accepts celiac disease as the infantile analog of sprue in adults is not a matter of indifference. Nothing is more certain than that the treatment of sprue with liver, first used by Bloomfield and Wycott in 1926 has completely altered the outlook in cases of this disease. Rhoads and Miller<sup>29</sup> have shown that even the most severe and resistant sprue yields promptly to what Almot called 'adequate liver therapy' and our experience confirms this in the most positive fashion. We believe that equally favorable results will follow the application of adequate liver therapy to celiac disease.

#### SUMMARY

From a detailed study of nine instances of the sprue syndrome the conclusion is reached that tropical sprue, nontropical sprue and celiac disease are identical in their etiology. An analysis of the separate components of the sprue syndrome reveals a clinical picture which is characteristic permitting ready and accurate differential diagnosis. Prompt improvement follows administration of liver in adequate amounts.

NOTE.—Since this paper was submitted for publication we have studied five additional instances of sprue. One patient of 17 showed typical dwarfism as described in this paper, the other four were adults. The study of these patients has served to confirm the conclusions which we have stated.

26 Fairley, N. H. Sprue. Its Applied Pathology, Biochemistry and Treatment, *Tr. Roy. Soc. Trop. Med. & Hyg.* **24** 131, 1930.

27 Scherer, E. Ein Fall von embryonischer Sprue, *Klin. Wchnschr.* **8** 1625 (Aug. 27) 1929.

28 Meyer, A. Ueber Coeliakie, *Ztschr. f. klin. Med.* **119** 667, 1932.

29 Rhoads, C. P., and Miller, D. K. Intensive Liver Extract Therapy of Sprue, *J. A. M. A.* **103** 387 (Aug. 11) 1934.

# EXTENSIVE ARTERIAL AND VENOUS THROMBOSIS COMPLICATING CHRONIC ULCERATIVE COLITIS

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It is generally agreed that chronic ulcerative colitis is one of the most serious of the diseases that afflict the digestive tract of man. Its complications may be equally serious. Fortunately, they are rare, but, unfortunately, when they do occur in a given case they are likely to be multiple.<sup>1</sup>

One of the very serious complications of chronic ulcerative colitis is extensive thrombosis of the blood vessels. Among fifteen hundred cases of chronic ulcerative colitis which we have observed thrombophlebitis or arterial thrombosis which was extensive enough to become a grave clinical problem occurred in eighteen. Less serious subclinical thrombosis of small vessels, chiefly the veins, has occurred more frequently than extensive thrombosis. In patients who come to necropsy, emboli and thrombi have been found in various places, such as the pelvic plexuses, lungs, spleen and kidneys. Among the last forty-three of our patients who died of chronic ulcerative colitis, emboli and thrombi were found in fourteen.

The six cases reported here have been under our observation in the last two years, whereas nine other cases have been observed in the eight prior years. This suggests an increased incidence of this complication and made this report seem timely. Because some of these patients received the anticolitis serum, some observers might suggest that the thrombosis occurred as a result of its administration, however, in one case, in which the thrombosis was severe, the patient did not receive any serum, and this phenomenon has occurred in many other cases in which serum was not employed.

## REPORT OF CASES

CASE 1—A man, aged 26 years, came to the Mayo Clinic on Dec. 2, 1933 because of severe chronic ulcerative colitis, which had been present for a year. The condition had been progressive. His normal weight was 135 pounds (61.2 Kg.). He was a husky, athletic person, a university graduate and a teacher. Since his

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From the Division of Medicine, the Mayo Clinic.

1. Bargaen, J. A. *The Management of Colitis*, edited by Morris Fishlein. Garden City, N. Y., Doubleday, Doran & Company, Inc., 1935.

condition had been progressive, a cecostomy was performed elsewhere on July 28, 1933. However, this was not followed by the desired improvement, so that when he arrived at the clinic he was having between fifteen and twenty-five stools and rectal discharges daily, containing much pus and quantities of blood, both liquid and clotted. His weight was 104 pounds (47.2 Kg). There was moderate secondary anemia. The value for the hemoglobin was 7.5 Gm per hundred cubic centimeters of blood. There were 3,310,000 erythrocytes and 9,200 leukocytes per cubic millimeter of blood. Of the total number of leukocytes, 34 per cent were nonfilamented polymorphonuclear neutrophils and 22 per cent were filamented polymorphonuclear neutrophils. Many stools were examined, and no parasites, ova, acid-fast bacilli or unusual bacteria were found. The proctoscopic examination revealed the usual picture of an ulcerated, granular mucous membrane which bled easily. The activity was 3, on a basis of 4, and the lumen was limited in some places to 1.5 cm. Roentgenologic examination of the colon revealed extensive and advanced disease of the entire colon.

The specific antibody solution was administered intramuscularly, the opening produced by the cecostomy was allowed to close, and two blood transfusions (one on December 6 and one on December 11) were given. Improvement was slow but progressive, and by Jan. 1, 1934, the administration of the autogenous vaccine was begun. The patient was dismissed on February 1. At that time he was greatly improved clinically and weighed 155 pounds (70.3 Kg), although he was still averaging about ten stools daily, which did not contain any blood. Two weeks before his dismissal the value for the hemoglobin was 9.2 Gm per hundred cubic centimeters of blood and there were 4,320,000 erythrocytes and 5,500 leukocytes per cubic millimeter of blood.

He continued to improve until three weeks after returning home, at which time pain developed in the left popliteal space. One week later he noted numbness and coldness in the left foot and cyanosis of the toes. Two weeks later he returned to the hospital in Rochester. At that time examination revealed that the left foot was definitely colder than the right, abnormally pale when elevated and abnormally red when dependent. There was some diminution of sensation and muscle power of the left leg and absence of pulsation in the left femoral, popliteal, posterior tibial and dorsalis pedis arteries. The pulsations were normal in the right leg. A diagnosis of progressive thrombosis of the left popliteal and femoral arteries, with secondary ischemic neuritis was made. Several blood cultures on successive days at that time did not reveal any organisms. The temperature, which rarely had gone above 100 F during his previous stay in the hospital, averaged 102 F. Ten days after his admission the patient complained of the right foot "going to sleep," and within twelve hours this foot was found to be white and cold, with collapsed veins. There were normal pulsations in the right femoral artery, but the pulsations in the right popliteal artery were diminished. There was no pulsation in the dorsalis pedis and posterior tibial arteries. Three days later pulsations had disappeared in the popliteal and femoral arteries and the leg was cold and cyanotic to 6 inches (15 cm) above the knee. There were severe pain and inability to move the foot and toes. The plasma coagulability index (Nygaard-) was normal (11), and the number of blood platelets was also normal, 370,000 per cubic millimeter. On the next day the left leg and foot became more painful and cyanotic than they had been. At the end of another week there was dry gangrene of the sole of the right foot. Two weeks later there was well delimited

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2 Nygaard, K. K. Coagulability of the Blood Plasma, Proc. Staff Meet., Mayo Clin. 7:544 (Sept. 21) 1932.

dry gangrene of both legs and feet, which extended above the knees (fig 1). Because of pain and increasing toxemia, amputation of the legs seemed unavoidable and was undertaken on April 16. For two days the patient seemed to rally, but after that failure was progressive, and he died on April 22, six weeks after the onset of the arterial occlusion.

Examination of the amputated legs showed that all the large arteries and veins of the legs were completely occluded by gray-red thrombi. Histologic examination of the lower part of the femoral arteries, the popliteal arteries and the upper part of the posterior tibial arteries showed that the thrombi consisted of degenerated fibrin and erythrocytes, they contained practically no cell nuclei, and there was no evidence of organization. The arterial walls appeared normal and did not disclose any reaction. The thrombus in the left popliteal vein was partly organized at the margin and in a band across the center. The media and adventitia of the vein showed moderate infiltration with histiocytes and fibroblasts. The right



Fig 1—Extensive dry gangrene of the legs, a result of arterial thrombosis.

popliteal vein was filled with disintegrating debris and polymorphonuclear leukocytes, and there was marked irregular infiltration of the wall of the vein with polymorphonuclear leukocytes. The picture was that of simple thrombosis of the arteries and of suppurative thrombosis of the right popliteal vein, which probably was secondary to the more distal gangrenous process. There was no pathologic evidence of thrombo-angitis obliterans, and there was no evidence of arteriosclerosis.

At necropsy there was found to be complete thrombosis of both iliac and both femoral arteries and of the abdominal aorta, which extended above the origin of the renal arteries, which also were completely thrombosed (fig 2). There was partial infarction of the right kidney and complete infarction of the left kidney. There also was thrombosis of both iliac and both femoral veins, the inferior vena cava and the left renal vein. Arteries in the lower lobes of both lungs were found to be occluded by partially organized thrombi (probably emboli originally). Histologic examination of the aorta and of the iliac arteries revealed a degenerated, homogeneous acellular thrombus, but there was no organization. There were slight



infiltration of the arterial walls with lymphocytes and fibroblasts and moderate dilatation and congestion of the vasa vasorum. In the iliac veins the picture was the same, except that the thrombi were definitely organized at their margins and there were a few small collections of polymorphonuclear leukocytes in the region of the intima. On the basis of the histologic findings, the oldest thrombosis was probably in the left popliteal and femoral veins, although this had not been apparent clinically (fig. 3).

This is the only case on record in which there was progressive arterial thrombosis in connection with advanced chronic ulcerative

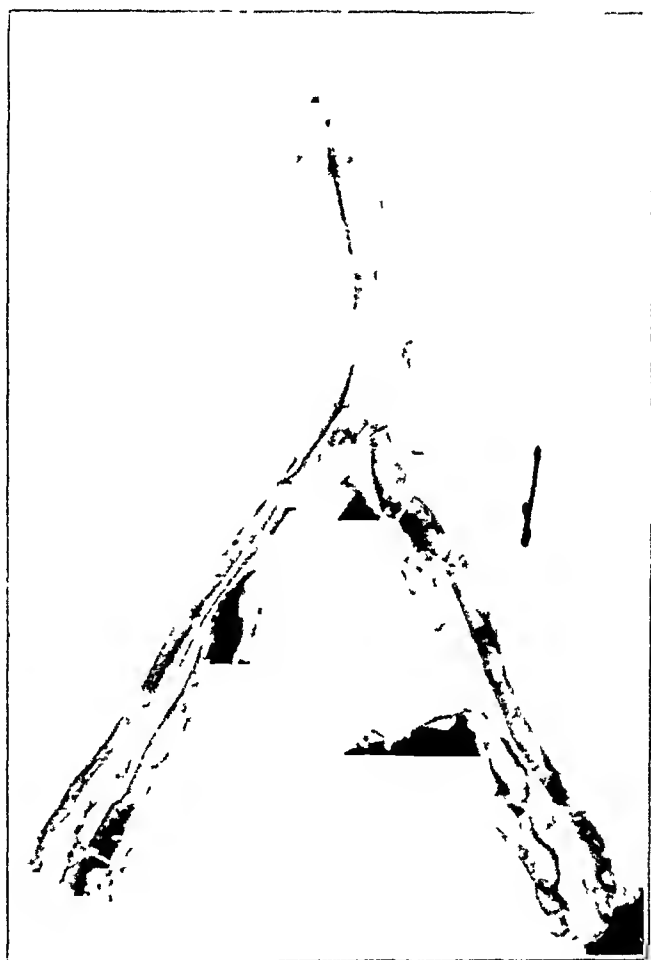


Fig. 2—Extensive thrombosis of the aorta and the iliac arteries

colitis. Observation of the clinical picture in such a case is most distressing. We are frankly pleased that this complication is such a rare one.

**CASE 2**—A single woman, aged 21, came to the clinic on Nov. 25, 1934, on account of severe chronic ulcerative colitis which had been present for five months. The condition had become progressively worse from the time of its onset. The patient had lost 30 pounds (13.6 Kg.) in weight. She was averaging about one dozen rectal discharges every twenty-four hours. The stools consisted chiefly of large quantities of fresh and clotted blood and pus. A proctoscopic examination revealed the typical picture of chronic ulcerative colitis with marked activity.

She was too ill at that time to warrant roentgenologic examination. The temperature was 102 F at the time of her admission. The value for the hemoglobin was 7 Gm per hundred cubic centimeters of blood. There were 3,830,000 erythrocytes and 12,200 leukocytes per cubic millimeter of blood. Of the leukocytes 71 per cent were polymorphonuclear neutrophils, divided on the basis of all leukocytes present as follows: 48 per cent nonfilamented and 23 per cent filamented. Treatment with the specific antibody solution (concentrated serum) was begun at once, and during the first week it was necessary to administer dextrose solution intravenously because the patient was unable to take anything by mouth. A transfusion of 250 cc of blood was also given. Improvement was slow but progressive.

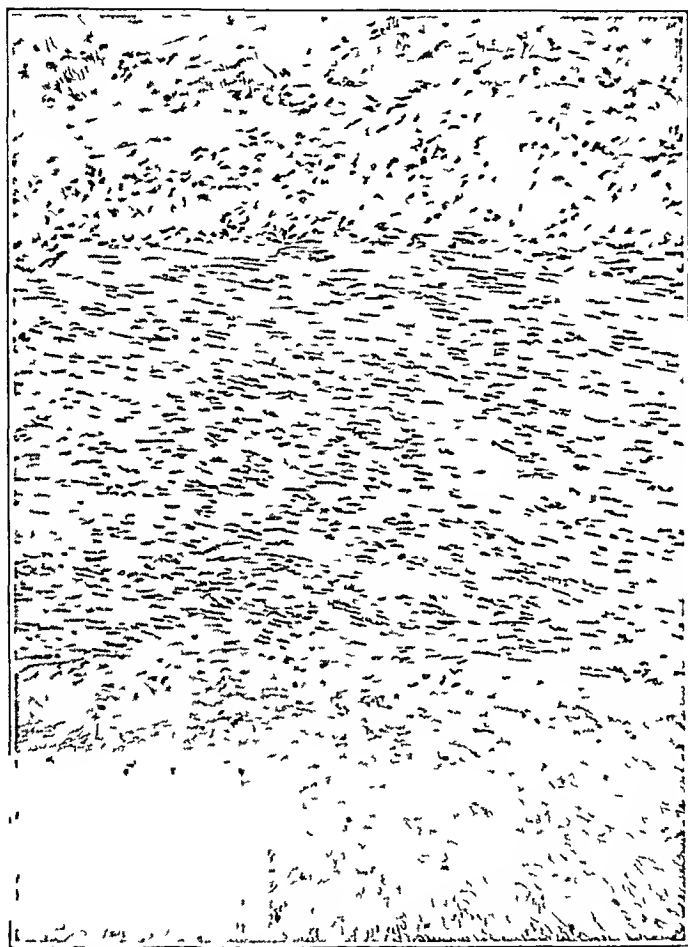


Fig 3—Photomicrograph of a histologic section of the left external iliac artery, showing almost complete absence of organization of the thrombus and of inflammatory reaction in the arterial wall. Hematoxylin and eosin stain,  $\times 85$ .

by the end of the month the bleeding had stopped and the value for the hemoglobin had increased to 9.3 Gm per hundred cubic centimeters of blood. At that time there were 4,410,000 erythrocytes per cubic millimeter of blood but there were still 12,400 leukocytes per cubic millimeter. Sixty-one per cent of the leukocytes were nonfilamented polymorphonuclear neutrophils and 13 per cent were filamented polymorphonuclear neutrophils. For several weeks the condition seemed stationary and the rectal discharges numbered five in twenty-four hours at a maximum. On December 29, thirty-five days after her admission to the hospital, signs of thrombophlebitis developed in the lower part of the right leg.

There were pain and some swelling. Four days later both legs became markedly swollen and painful and there was definite pitting edema. The superficial veins were prominent and distended, and there were dilated superficial veins over the right lower quadrant of the abdomen. The temperature, which had previously been elevated to 101 F in the afternoon, fell to 97 F. The pulse rate rose to 130. The legs were elevated, and hot packs were applied. The edema of the legs disappeared partly but not completely. Pain became less marked than it had been, but the patient became progressively weaker and her condition was more toxic than before. It is of note that the plasma coagulability index

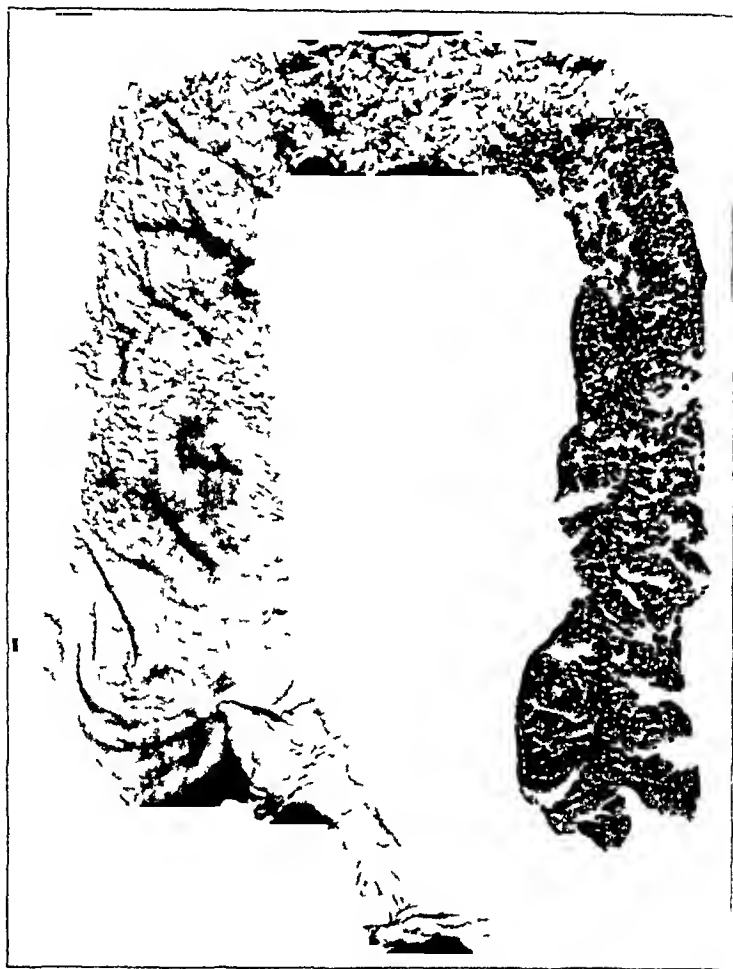


Fig. 4—Extensive advanced and destructive chronic ulcerative colitis

(Nygaard) was definitely elevated (14) forty-eight hours after the onset of the thrombophlebitis, the number of blood platelets was 600,000 per cubic millimeter at that time. Seven days later the plasma coagulability index was the same as it was at that time and the blood platelets numbered 262,500 per cubic millimeter of blood. Three days before death the plasma coagulability index was 18 and there were 130,000 blood platelets per cubic millimeter. The value for the hemoglobin had dropped to 5.6 Gm per hundred cubic centimeters of blood, and the number of erythrocytes had decreased to 3,190,000 per cubic millimeter. When death occurred, on Jan. 18, 1935, the chronic ulcerative colitis was found to be massive and extremely destructive and to involve the entire colon and terminal portion of the ileum (fig. 4). A gray-white thrombus, which was firm and adher-

ent, filled the lower portion of the inferior vena cava. The thrombus extended from the level of the left renal vein (fig 5), into which it projected to the bifurcation of the inferior vena cava and thence into the common iliac veins, into the external iliac vein and into the hypogastric veins, filling all these veins.

Gray thrombi (emboli) were found also in the arteries to the upper lobe of the right lung and to the lower lobe of the left lung.

Histologic examination of the vena cava and iliac veins revealed that the majority of the thrombi consisted of degenerated blood and fibrin, with few cell nuclei. The margins of the thrombi were made up of erythrocytes and a few



Fig 5—Extensive thrombosis of the inferior vena cava and of the common iliac veins.

fibroblasts and were adherent to the walls of the veins. Small collections of lymphocytes and a few fibroblasts were scattered through the walls of the veins, chiefly in the inner circular layer of the muscle. The vasa vasorum appeared normal. The picture suggested primary thrombosis with slight secondary reaction in the wall of the vein. The thrombi in the pulmonary arteries were attached to the arterial wall only at one small area and showed definite organization at that point, which suggested that they were emboli that were several days old.

CASE 3—A married woman, aged 31, was brought to the hospital in an ambulance on April 23, 1934. She had had diarrhea for twenty-nine years, or since the age of 2 years. This followed a severe attack of scarlet fever. She could not

recall having had less than from six to eight bowel movements in twenty-four hours. The stools were watery and contained various quantities of blood. Occasionally there were severe exacerbations, during which she had many purulent bloody rectal discharges every twenty-four hours. In spite of this, she enjoyed rather good health, attended school, played and grew, and her weight was about the average for a child of her age. She consulted numerous physicians and had various treatments. Her maximal weight was 127 pounds (57.6 Kg). In October 1933 she commenced to lose strength and weight, became very pale and had attacks of abdominal bloating and severe cramplike pain. The pain was situated in the left half of the abdomen and often was colicky. After that, there was more blood in the stools than there had been before. In December 1933, edema of the ankles and the legs appeared and extended to the knees. There also was a slight edema of the hands and some dyspnea. The physician whom she consulted in January 1934 ordered her to bed at once and advised a high caloric diet which she then followed. When her condition warranted it, he made a proctoscopic examination and was the first to make a diagnosis of chronic ulcerative colitis. She was very ill, there were periods of continuous vomiting and then there was some improvement. However during the two weeks before she came to the clinic, she again became worse than she had been. At that time there were some vomiting and signs of obstruction. At the time of her admission to the hospital which was at 6:30 p. m., her weight was 104 pounds (47.2 Kg), she appeared very pale, the pulse was rapid, the abdomen was distended slightly and there was tenderness in the left lower quadrant. At 8:30 p. m. she was suddenly seized with excruciating pain in the left lower quadrant of the abdomen. That portion of the abdomen became exquisitely tender. Symptoms of shock developed, the pulse became rapid and thready, and the temperature was 101 F. A diagnosis of chronic ulcerative colitis with perforation of the sigmoid flexure was made. Because of the history of obstruction and the marked change in symptoms a superimposed neoplasm was suspected.

The foot of the bed was elevated, sedatives were administered, nothing was allowed by mouth and complete rest was instituted. Twelve hours later a huge mass appeared in the left lower quadrant of the abdomen. The aforementioned symptomatic measures were continued, and the fluid balance of the body was maintained by the intravenous administration of dextrose solution. The mass rapidly decreased in size, and the symptoms of perforation seemed to subside.

She had definite anemia, the value for the hemoglobin was 8.5 Gm. per hundred cubic centimeters of blood, and the erythrocytes numbered 4,480,000 per cubic millimeter. On the fifth day after her admission to the hospital pain and tenderness developed in the calf of the left leg. There was some swelling of the ankle also. Twenty-four hours later there was pain in the left thigh and groin, marked swelling of the entire leg and congestion and dilatation of the superficial veins (fig. 6). Tenderness in the calf of the right leg was also noted for a short period. There was no increase in temperature or pulse rate. Elevation of the limb and the application of hot packs improved the condition, but two days later there was another attack of severe generalized abdominal pain and a concomitant severe pain in the calf of the left leg. The foot became cold and very cyanotic.

Pulsations were present in the femoral artery but were not felt in the dorsalis pedis artery, although the huge swelling of the leg made the accuracy of palpation questionable. The patient died twenty-four hours later, seven days after her admission to the hospital. It is noteworthy that after each daily intravenous injection of a solution containing 10 per cent dextrose and 1 per cent sodium chloride thrombosis developed at the site of injection.

Necropsy revealed a very advanced, destructive chronic ulcerative colitis of the entire colon. There was complete obliteration of any demarcation of the ileocecal junction. A polypoid carcinoma of the sigmoid flexure and a mucoid

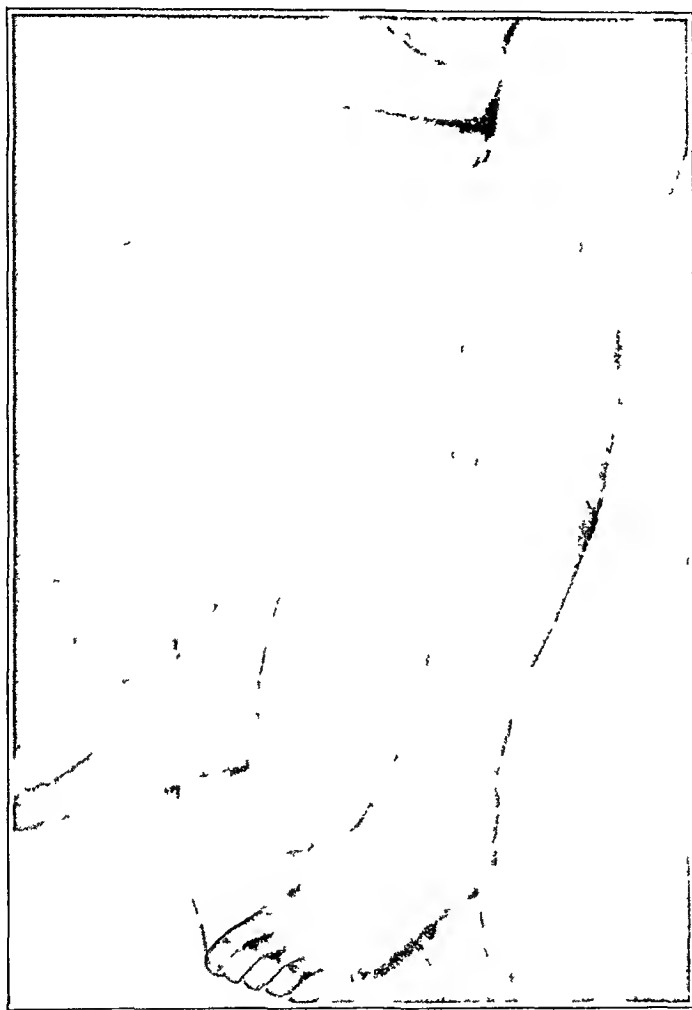


Fig 6—Extensive thrombophlebitis of the left iliac vein showing massive swelling of the entire leg and marked congestion of the skin (infra-red photograph)

carcinoma of the splenic flexure were also present (fig 7). The entire left common iliac, the left hypogastric, the left external iliac and the left femoral vein were found to be occluded by gray-red friable thrombi. A small infarct was found in the lower lobe of the right lung.

Histologic examination of the iliac veins revealed that the thrombi consisted almost entirely of fibrin and erythrocytes (fig 8). There was early fibroblastic organization at the margins only, and no inflammatory reaction was present in the walls of the veins.

CASE 4—A single woman, aged 24, was brought to the clinic in an ambulance on Dec 24, 1933. She had symptoms of severe and very active chronic ulcerative colitis. The maximal number of rectal discharges in twenty-four hours, during the first week of her stay in the hospital, was eighteen. The temperature ranged between 101 and 102 F daily. The rectal discharges consisted largely of bloody purulent material. The blood was red, fresh and clotted. A proctoscopic examination suggested the activity to be 2, on the basis of 4. It was not until January 18 that a roentgenologic examination of the colon seemed warranted, this revealed destructive chronic ulcerative colitis of the entire colon. The value for the hemo-



Fig 7—Markedly destructive chronic ulcerative colitis with (I) a polypoid carcinoma of the sigmoid flexure and (II) an annular scirrhous carcinoma of the transverse colon

globin at the time of her admission was 66 Gm per hundred cubic centimeters of blood. There were 3,360,000 erythrocytes and 25,200 leukocytes per cubic millimeter of blood. Of these, 70 per cent were nonfilamented polymorphonuclear neutrophils and 15 per cent were filamented polymorphonuclear neutrophils. The rate of sedimentation was markedly increased, being 160 mm in a two hour period. Microscopic examination of the rectal discharges failed to reveal parasites or ova, but a pure culture of the diplostreptococcus grew in the cultures. Roentgenologic examination of the chest did not reveal any disease. Specific antibody

solution (concentrated serum) was administered intramuscularly, and two blood transfusions were given, one on the fourth and one on the tenth day of the patient's stay in the hospital. The fever gradually receded, so that by the eighteenth day in the hospital the temperature was normal. On the twenty-first day, severe pain in the right lower part of the abdomen occurred, with a subsequent rise in the temperature. During the next two weeks, there was fever, the lowest temperature was 102.5 F, and the maximal was 105 F. Two weeks after the onset of this attack pain occurred in the left lower quadrant of the abdomen. This pain had all the features of that caused by acute colonic perforation. Dextrose solution was



Fig. 8—Photomicrograph of histologic section of left iliac vein, showing almost complete lack both of organization of the thrombus and of inflammatory reaction in the wall of the vein. Hematoxylin and eosin stain,  $\times 125$ .

administered intravenously, no fluid was administered by mouth and a solution of gentian violet and serum was administered intravenously. On February 16, fifty-six days after her admission to the hospital, a swelling of the entire left leg and thigh developed (fig. 9). This abated after the leg had been elevated for a few days. On February 22, the right leg became markedly swollen and edematous, with areas of ecchymosis and dilatation of the superficial veins. Six days later, another sudden attack of severe pain developed in the right lower quadrant of the abdomen. The pain extended around to the back. She vomited and became very pale, but there was no rise in the temperature or the pulse rate.



After a long and stormy course the patient completely recovered. She had passed through a state of what was considered clinically to be massive bilateral thrombophlebitis of the iliac and femoral veins and possibly a subsequent intra-abdominal thrombophlebitis. She also had passed through a stage of subacute colonic perforation. She was dismissed on March 3, 1934. Subsequent reports indicated satisfactory progress, the latest of these being on May 28, 1936.

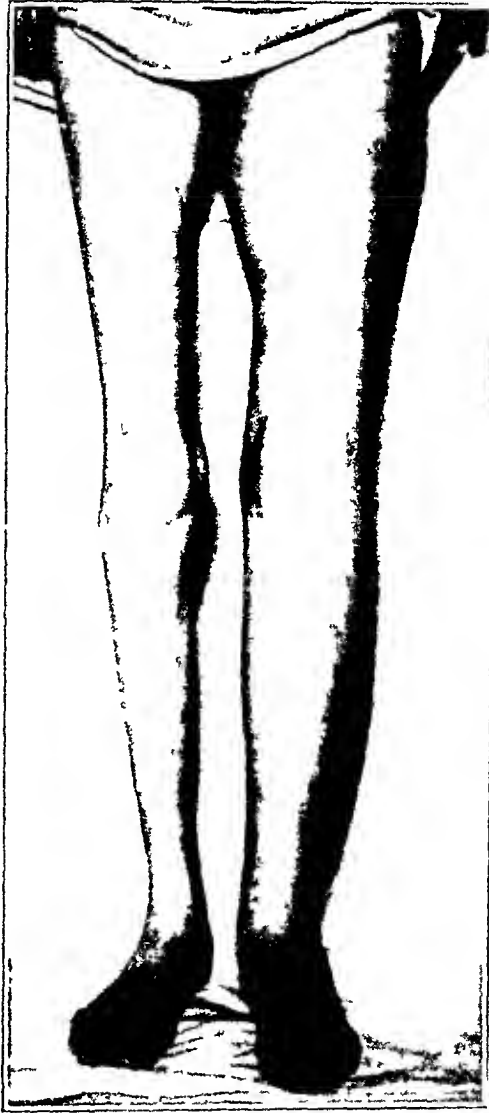


Fig. 9—Thrombophlebitis of the left iliac vein showing swelling of the entire leg and dilated prominent superficial veins, particularly of the thigh (intra-red photograph)

CASE 5—A youth, aged 19 years, was brought to the hospital because of severe chronic ulcerative colitis, which had been present for eight months. While serving as a caddy on a golf course, he suddenly was seized with cramps and a desire to defecate. A stool which was passed at that time contained blood. His symptoms became progressively worse. At the time of his admission to the hospital, he was averaging twelve bloody, purulent rectal discharges daily. The

activity of the disease, from a protoscopic standpoint, was 2, on the basis of 4 Ten successive examinations of the stools, on as many days, failed to reveal any parasites or unusual bacteria except the diplostreptococcus of chronic ulcerative colitis. A roentgenologic examination of the colon was not made because of the severe, systemic reaction of the disease. There was daily fever during his stay in the hospital, and marked anemia. The lowest value for the hemoglobin was 4.86 Gm per hundred cubic centimeters of blood. There were 2,350,000 erythrocytes per cubic millimeter of blood. The normal weight had been 118 pounds (53.5 Kg). The weight at the time of admission was 85 pounds (38.6 Kg). The specific antibody solution (concentrated serum) was administered, and one blood transfusion was given. The patient made slow but progressive improvement.

On the twenty-seventh day after his admission to the hospital, a massive swelling of the left leg developed. This responded to some extent to elevation of the limb and to the application of hot packs. The patient left the hospital five days later, to continue treatment at home. The clinical picture was that of thrombophlebitis of the left iliac vein, which complicated severe chronic ulcerative colitis.

CASE 6—A man, aged 22, came to the clinic on May 23, 1934, because of rather severe chronic ulcerative colitis, which had been present for five months. He had been having fifteen bowel movements daily for several months. There was loss of weight and general wasting and an increase in the temperature each afternoon. The amount of blood in the stools was not great. At the time of his admission to the hospital he was averaging between eight and nine stools daily, but he appeared more ill than this might suggest. Proctoscopic examination revealed the typical picture of chronic ulcerative colitis, and roentgenologic examination revealed involvement of the entire colon. Roentgenologic examination of the thorax did not reveal any disease. The value for the hemoglobin was 13.3 Gm per hundred cubic centimeters of blood. There were 4,380,000 erythrocytes and 10,700 leukocytes per cubic millimeter of blood. Of the total number of leukocytes, 37 per cent were nonfilamented polymorphonuclear neutrophils and 20 per cent were filamented polymorphonuclear neutrophils. The sedimentation rate was greatly increased, reaching 118 mm in two hours. The urine was essentially normal. On the sixth day of his stay in the hospital his temperature rose to 103 F and the number of leukocytes increased to 16,600 per cubic millimeter. At that time cyanosis and marked swelling of the entire left leg appeared. There was pain and tenderness in the groin and distention of the cutaneous veins of the thigh and the lower part of the abdomen. A diagnosis of thrombophlebitis of the left femoral and iliac veins was made. Two weeks later thrombophlebitis appeared in the upper part of the long saphenous vein. This gradually descended to the knee. The vein was very tender, swollen and indurated, and the skin over it was red. Four days later thrombophlebitis developed in the right median basilic vein at the site of a venipuncture and spread up the vein for a distance of 10 cm. On the fourteenth day after the onset of the iliac thrombophlebitis, the coagulability index of the plasma was 1.3 and the blood platelets numbered 750,000 per cubic millimeter.

After a month of treatment by elevation of the limb, the application of hot moist packs to the leg and the application of roentgenotherapy to the long saphenous vein, the pain, local tenderness and almost all the swelling of the leg disappeared, and the patient was allowed to be out of bed.

The treatment of the colitis included the administration of the specific antibody solution (concentrated serum) as well as the usual diet and the administration of anticolitis vaccine. Complete relief from symptoms of colitis followed, and a report on May 1, 1935, revealed that the patient has remained well.

## COMMENT

It is of interest that all these patients were young adults, between the ages of 19 and 31 years. At the time of the development of the thrombosis, the patients had been at rest in bed for several days or weeks and therefore were subjected to venous stasis in the lower extremities. All except one had rather marked secondary anemia. In all these cases large veins, such as the femoral and iliac veins and even the vena cava, were involved. All these patients had severe chronic ulcerative colitis, with fever and evidence of toxemia. Colonic perforation occurred in two of the six cases. The roentgenograms, in those cases in which roentgenologic examination was possible, revealed extensive intestinal disease. In our experience it is only in the cases of the most severe involvement in which there are very acute exacerbations of the disease that roentgenography seems inadvisable. The pathologic specimens which were obtained at necropsy illustrate further the immensely destructive colonic process in the cases in which death occurred. Local or even diffuse peritonitis, or at least peritoneal irritation, was also present in these cases.

The exact pathogenesis of venous thrombosis and thrombophlebitis is still debatable. Its occurrence as a complication of various severe infectious diseases<sup>3</sup> which are accompanied by generalized toxemia, particularly typhoid, pneumonia, and influenza, was reviewed by Welch<sup>4</sup> in 1898. It is also seen in association with anemia, some of the early cases that were described were associated with chlorosis, in which there was no evidence of infection. Rest in bed, with resultant venous stasis, is considered to be a factor in certain cases, particularly in those of postoperative thrombophlebitis (Robertson<sup>5</sup>). It is not surprising, therefore, that thrombosis of the veins of the legs should complicate chronic ulcerative colitis, in which all three factors—severe infection with toxemia, anemia and venous stasis—are present. As an inciting factor, there is the possibility of local damage to the large iliac veins, as the result of the neighboring peritonitis. Also, thrombi may form in small veins of the rectum close to ulcers and propagate through branches of the hypogastric to the common iliac veins. Arterial thrombosis has been described as a rare complication of typhoid, pneumonia and influenza, as well as of other infectious diseases. However, it has not been described as occurring in chronic ulcerative colitis, and such a

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3 Barker, N. W. General Classification of Diseases of Veins and Clinical Types of Thrombophlebitis, *Proc. Staff Meet., Mayo Clin.* 9:191 (March 28) 1934.

4 Welch, W. H. Thrombosis in Allbutt, Clifford, and Rolleston, H. D. *A System of Medicine*, New York, The Macmillan Company, 1909, vol. 6, p. 691.

5 Robertson, H. E. Pulmonary Embolism Following Surgical Operation, *Am. J. Surg.* 26:15 (Oct.) 1934.

progressive and extensive simple arterial thrombosis, with venous thrombosis as well, as was seen in case 1, is a very unusual event, and is rarely seen in a young person whose arteries otherwise are normal

The histopathologic picture and the location of the involvement chiefly in large venous trunks show that the thrombosis associated with chronic ulcerative colitis is out of all proportion to any changes which can be seen in the vessel walls. There may be some small focus of inflammation in a vessel which acts as a starting point, but the extensive propagation of the thrombus suggests that there is also an increased tendency of the blood itself to produce thrombosis. Such evidence of phlebitis or arteritis as is seen in the sections is minimal and can be interpreted as chiefly secondary to the presence of the thrombus. Attempts at organization of the thrombi are slow and rather feeble.

At the Mayo Clinic, in a series of cases of chronic ulcerative colitis, the incidence of massive thrombosis in the vessels of the legs was slightly more than 0.1 per cent. This complication must be regarded as of serious prognostic import. In three of the six cases which are reported the patient died. All the deaths were caused by toxemia and not by embolism. It seems probable that the thrombosis in such cases is caused by the combination of local infection, generalized toxemia, alterations in the blood and venous stasis.

# THERAPEUTIC EFFECT OF TOTAL ABLATION OF NORMAL THYROID ON CONGESTIVE FAIL- URE AND ANGINA PECTORIS

XVIII THE CARDIAC OUTPUT FOLLOWING TOTAL THYROIDECTOMY IN  
PATIENTS WITH AND WITHOUT CONGESTIVE HEART FAILURE,  
WITH A COMPARISON OF RESULTS OBTAINED WITH THE  
ACETYLENE AND ETHYL IODIDE METHODS

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AND

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BOSTON

Studies of the cardiac output in spontaneous myxedema are few. Various observers<sup>1</sup> have reported a decrease in the minute volume output of the heart in patients with hypothyroidism. The recently reported work of Blumgart and his associates<sup>2</sup> in establishing the value of total

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This investigation was aided by a grant from the William W. Wellington Memorial Research Fund of Harvard University.

From the Medical Service and Medical Research Laboratories of the Beth Israel Hospital and the Department of Medicine, Harvard University Medical School.

1 (a) Means, J. H. *Circulatory Disturbances in Diseases of the Glands of Internal Secretion*, *Endocrinology* **9** 192, 1925. (b) Mobitz, W. *Die Ermittlung des Herzschlagvolumens des Menschen durch Einatmung von Aethyljodiddampf*. IV. Klinisch kompensierte Veränderungen des Herzens und der Gefässe und beginnende Kreislaufdekompensation ohne Lungenveränderungen, *Deutsches Archiv für klin. Med.* **157** 359, 1927. (c) Kinnmonth, J. G. *The Circulation Rate in Some Pathological States, with Observations on the Effect of Digitalis*, *Quart. J. Med.* **21** 277, 1927. (d) Bansi, H. W. *Die Kreislaufgeschwindigkeit beim Morbus Basedow und Myxoedem*, *Klin. Wchnschr.* **7** 1277, 1928. (e) Bansi, H. W., and Groscurth, G. *Die Kreislauleistung beim Basedow und Myxoedem*, *Ztschr. für klin. Med.* **116** 583, 1931.

2 Blumgart, H. L., Levine, S. A., and Berlin, D. D. *Congestive Heart Failure and Angina Pectoris. The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity*, *Arch. Int. Med.* **51** 866 (June) 1933. Blumgart, H. L., Riseman, J. E. F., Davis, D., and Berlin, D. D. *Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris. III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity*, *Arch. Int. Med.* **52** 165 (Aug.) 1933. Blumgart, H. L., Berlin, D. D., Davis, D., Riseman, J. E. F., and Weinstein, A. A. *Total Ablation of Thyroid in Angina Pectoris and Congestive Failure. XI. Summary of Results in Treating Seventy-Five Patients During the Last Eighteen Months*, *J. A. M. A.* **104** 17 (Jan. 5) 1935.

ablation of the thyroid gland in the treatment of chronic intractable cardiac disease made it advisable to study the cardiac output and related aspects of the circulation in hypothyroidism induced by this operation. Data obtained by the acetylene method<sup>3</sup> for seven patients with no evidence of congestive failure were reported in a previous publication.<sup>4</sup> This communication presents preoperative and postoperative studies of the cardiac output by means of the ethyl iodide method<sup>5</sup> in patients with and without congestive failure on whom total thyroidectomy was performed. Results obtained by this method and by the acetylene method in the same patients are compared.

#### MATERIAL AND METHODS

Observations have been made on twenty-three patients in whom hypothyroidism developed subsequent to total ablation of the thyroid gland. Eleven patients had no history or signs of congestive heart failure, these patients were operated on for the relief of angina pectoris (cases 1, 2, 3, 5, 6, 7, 8, 9, 10), for latent hyperthyroidism with angina pectoris (case 11) or for the control of severe diabetes (case 4). Of this group five subjects were men and six were women, the ages varied from 23 to 65 years. Another group, consisting of twelve patients (cases 12 to 23), were operated on for the relief of congestive failure. Of these, nine were men and three were women, the ages varied from 23 to 66 years. The preoperative measurements were made shortly before operation, when the patients were in the best possible condition, i. e., after they had had a period of rest in bed and had received full therapeutic doses of digitalis and in most instances intravenous injections of salyrgan as well. There was no perceptible edema of the extremities and at most very few râles over the bases of the lungs, slight or moderate enlargement of the liver was present in many patients at the time the measurements reported here were made. The hemoglobin content was 85 per cent or higher in all the patients studied. Many patients showed slight or moderate sclerosis of the peripheral arteries, the blood pressure in most of these instances was elevated.

In determining the cardiac output by the acetylene method the following procedure was used. All measurements were made with the patient in the post-absorptive state, under basal conditions, in the semirecumbent position, after a rest of from one-half to one hour. The basal metabolic rate was first measured in duplicate with a Collins-Benedict-Roth spirometer and calculated according to the Aub-DuBois normal standards. The arterial blood pressure was next measured with a mercury manometer with the standard cuff. The figures in the table represent the averages of several readings. The pulse rate was counted twice before each measurement of the cardiac output. Two measurements of the arteriovenous

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3 Grollman, A., Friedman, B., Clark, G., and Harrison, T. R. Studies in Congestive Heart Failure. XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, *J. Clin. Investigation* **12** 751, 1933.

4 Altschule, M. D., and Volk, M. C. The Minute Volume Output and the Work of the Heart in Hypothyroidism, *J. Clin. Investigation* **14** 385, 1935.

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TABLE 1—Data on Patients without Congestive Failure

Case	Age, years	Basal Meta-bolic Rate, Devia-tion from Normal, Percent	Oxygen Con-sump-tion, Ce per Minute	Arterio-venous Differ-ence, Volume per Cent	Cardiac Output, Liters	Cardiac Index	Pulse Rate	Car-diac Output per Beat, Ce	Blood Ve-loety, Arm to Toe	Arte-rial Pres-sure, Sys-tolic, Mm Mer-cury	Arte-rial Pres-sure, Dias-tolic, Mm Mer-cury	Vital Capacity, Ce per Sq. Meter	Work per Minute, per Kilo-gram Meter	Method*	Comment		
1	65	-35	167	6.50	2.6	1.3	58	44	16	6.9	120	76	1,150	3.4	59	A	14 months after operation, thy-roid $\frac{1}{10}$ grain (0.006 Gm.) daily
		-31	178	6.15	2.9	1.4	64	45	21	5.0	130	76	1,250	4.1	63	EI	23 months after operation thy-roid $\frac{1}{10}$ grain (0.006 Gm.) daily
2	53	-23	155	5.90	2.6	1.6	65	41	20		136	88	1,280	4.0	61	EI	22 months after operation, thy-roid $\frac{3}{10}$ grain (0.018 Gm.) three times a day
3	53	-28	133	6.70	2.1	1.3	65	32	7.4	186	110		940	4.1	64	A	11 months after operation, thy-roid $\frac{1}{10}$ grain (0.006 Gm.) daily
		-17	133	6.00	2.6	1.6	81	33	18	6.0	170	110	1,250	4.9	61	EI	16 months after operation, thy-roid $\frac{1}{10}$ grain (0.006 Gm.) twice a day
4	23	-10	179	5.80	3.1	2.0	71	42	10		114	60	2,000	3.5	48	A	3½ months after operation, thy-roid 5 grains (0.324 Gm.) daily
		-20	161	5.80	2.8	1.8	55	50	15	±0	124	80	2,100	3.9	70	A	4 months after operation, no thyroid for 2 weeks
		-15	166	5.80	3.0	1.9	87	34			110	60	1,800	3.5	40	EI	15 months after operation, thy-roid $\frac{1}{10}$ grain (0.006 Gm.) daily
5	53	-34	154	6.95	2.2	1.2	56	40	31		110	90	1,330	3.0	54	A	4 months after operation
		-15	193	5.85	3.3	1.9	79	42	22		116	86	1,530	4.5	53	A	5 months after operation, thy-roid 1 grain 3 times a day
		-29	165	6.35	2.6	1.4	76	34	37	3.1	104	76	1,330	3.2	42	A	9 months after operation thy-roid $\frac{1}{4}$ grain (0.016 Gm.) every 3 days

		-19	189	6 10	3 1	1 7	68	45	23		104	72	1,580	3 7	54	EI	14 months after operation, thy roid $\frac{1}{4}$ grain (0.016 Gm) three times a day
6	53	-37	133	5 85	2 3	1 4	55	41	32		130	86	2,200	3 3	61	A	4 months after operation
		-30	148	6 30	2 4	1 5	57	41	20	6 7	114	80	1,860	3 2	55	EI	13 months after operation, thy roid $\frac{1}{10}$ grain (0.006 Gm) daily
7	65	-36	160	6 35	2 5	1 2	46	35	21	4 1	138	90	1,890	3 9	85	A	10½ months after operation, thy roid $\frac{1}{10}$ grain (0.006 Gm) daily
8	57	-3	163	5 95	2 7	2 0	73	38	18	8 0	160	90	1,100	4 7	64	A	Before operation
		-22	135	6 23	2 2	1 5	74	29	21	7 7	164	102	1,080	3 9	53	A	4 months after operation, no thyroid for 5 weeks
		-34	118	6 95	1 7	1 1	63	27	27	8 9	150	94	1,010	2 3	45	A	4½ months after operation, no thyroid for 7 weeks
		-13	149	6 23	2 4	1 7	78	31			140	90	1,100	3 8	48	EI	9 months after operation, thy roid $\frac{1}{10}$ grain (0.006 Gm) and $\frac{2}{10}$ grain (0.012 Gm) on alternate days
9	57	-11	184	5 00	3 7	2 1	68	54	13	6 0	160	100	1,100	6 5	96	A	Before operation
		-25	156	6 67	2 3	1 4	60	39	23		140	82		3 4	57	A	6 weeks after operation
		-22	163	6 20	2 6	1 5	69	33			140	80	980	3 9	57	A	4 months after operation, thy roid $\frac{1}{10}$ grain (0.006 Gm) twice a day
10	59	-4	230	6 15	3 8	2 0	73	52	16	8 1	150	100	1,450	6 5	89	EI	Before operation
		-18	197	6 10	3 2	1 7	73	44	21	6 6	132	84		4 7	64	EI	3 months after operation, thy roid $\frac{1}{10}$ grain (0.006 Gm) daily
11	56	-2	223	5 80	3 8	2 2	70	55	13	9 1	150	90		6 2	89	EI	Before operation
		-17	180	6 10	2 9	1 6	58	50	17	7 7	150	90		4 7	81	EI	8 weeks after operation

^ Indicates measurements of the cardiac output by means of the acetylene method  
EI Indicates such measurements made by means of the ethyl iodide method



oxygen difference were made by the acetylene method of Grollman, Friedman, Clark and Harrison<sup>3</sup> The values reported represent the average of two or more measurements made at the same level of basal metabolism The maximum deviation from the average for any one value of the arteriovenous oxygen difference accepted as reliable was  $\pm 77$  per cent, and the average deviation from the values reported was  $\pm 33$  per cent The minute volume output of the heart was calculated from the arteriovenous oxygen difference and the oxygen consumption, the latter being estimated from data obtained during the measurement of the basal metabolic rate The venous pressure was then measured by the direct method of Moritz and von Tabora,<sup>6</sup> and finally the velocity of blood flow was estimated, the index used being the "arm to tongue" circulation time measured with decholin (sodium dehydrocholate)<sup>7</sup> The figures for the velocity of blood flow are the averages of two or more readings which did not differ from each other by more than two seconds In three instances the velocity of blood flow was not measured on the same day as the cardiac output The work of the left ventricle was calculated, the formula of Evans and Matsuoka<sup>8</sup> being used,  $W = QR + (wV^2/2g)$ ,<sup>9</sup> disregarding the velocity component  $wV^2/2g$ , since it represents only from 1 to 3 per cent of the total work

When the measurements of the cardiac output were made by the ethyl iodide method, the procedure was similar to that described, except that the basal metabolic rate was determined by the Tissot method simultaneously with the cardiac output The values reported represent the average of two or more determinations of the cardiac output made at the same level of basal metabolism The average deviation from the values reported was  $\pm 49$  per cent In three instances values were accepted which differed from each other by slightly more than  $\pm 10$  per cent It was felt that these values were valid, since they were in harmony with other values obtained on the same patients at other times They were accepted, however, only because the basal metabolic rate in each instance was changing rapidly and no opportunity for further study at the same level of basal metabolic rate was available

The results obtained by the ethyl iodide and the acetylene method on the same patients agree with each other within  $\pm 5$  per cent (tables 1 and 2) However, in our hands the ethyl iodide method was the more satisfactory of the two It requires no period of training for the patient and no prescribed respiratory rate, rhythm and depth, so that determinations even on myxedematous patients are usually satisfactory The only unreliable results obtained by this method occurred in patients with severe dyspnea and, in rare instances, in patients with marked myxedema, in whom the respirations were so extremely slow and shallow that satisfactory samples of alveolar air were not obtainable

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6 Moritz, F, and von Tabora, D Ueber eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsches Arch f klin Med* **98** 475, 1910

7 Gargill, S L The Use of Sodium Dehydrocholate as a Clinical Test of the Velocity of Blood Flow, *New England J Med* **209** 1089, 1933

8 Evans, C L, and Matsuoka, J The Effect of Various Mechanical Conditions on the Gaseous Metabolism and Efficiency of the Mammalian Heart, *J Physiol* **49** 378, 1915

9  $W$  = work,  $Q$  = cardiac output per unit of time,  $R$  = arterial resistance (mean blood pressure  $\times 136$ ),  $V$  = velocity of blood in aorta,  $w$  = weight of blood,  $g$  = acceleration due to gravity

TABLE 2—Data on Patients with Congestive Failure

Case	Age, Years	Basal Meta-bolic Rate, Devia-tion from Normal, Percent age	Arterio-Oxygen Con-sump-tion, Ce per Minute	Oxygen venous Differ-ence, Volumes per Cent	Cardiac Output, Liters	Cardiac Index	Pulse Rate	Car-diac Output per Beat, Ce	Blood Ve-locity, Arm to Tongue Circu-lation, Time, Seconds	Arte-rial Pres-sure, Sys-tolic, Mm Mer-cury	Arte-rial Pres-sure, Diastolic, Mm Mer-cury	Vital Capacity, Ce per Sq Meter	Work per Kilo-gram meters	Comment
12	53	-20	199	7.28	2.8	1.4	69	40	36	110	80	2,100	36	27 months after operation
13	52	-30	160	7.81	2.1	1.2	66	31	41	130	90	1,800	31	2 years after operation
14	55	-34	145	6.72	2.1	1.3	59	36	31	168	102	1,720	39	2 years after operation
15	24	-31	138	7.00	2.3	1.3	51	44	53	108	70	2,100	28	2 years after operation, thyroid
16	23	-25	190	7.41	2.6	1.4	63	41	45	110	70	1,380	32	21 months after operation, thyroid
17	48	-14	207	5.90	3.6	1.9	69	32	26	180	120	1,100	73	13 months after operation, thyroid
		-18	197	6.69	2.9	1.5	71	41	35	230	140		73	18 months after operation, thyroid
18	32	-8	175	6.50	2.7	1.7	66	40	17	88	76	1,040	32	15 months after operation, thyroid
19	53	-34	163	6.86	2.4	1.3	53	45		150	90	1,650	39	7 months after operation
20	38	+1	268	8.84	3.0	1.6	71	60	42	120	70	1,800	64	Before operation
		-7	215	7.34	3.3	1.7	58	57	31	115	60		39	2 weeks after operation
		-21	192	8.07	2.4	1.3	52	46	43	110	60	1,800	53	3 weeks after operation
21	66	-9	218	6.90	3.2	1.8	75	43	22	135	85	1,900	52	Before operation
		-15	185	8.25	2.2	1.3	70	32	29	138	85	1,800	37	10 days after operation
22	48	-1	236	6.85	3.5	1.9	71	49	33	110	70	1,330	43	Before operation
		-12	217	7.03	3.1	1.7	71	43	44	100	70		36	3 weeks after operation
		-20	201	7.69	2.7	1.4	64	43	59	105	70		50	4 weeks after operation
		-27	179	8.18	2.3	1.2	53	41	53	105	70	1,240	27	5 weeks after operation
23	36	+0	179	6.90	2.6	1.8	41	65	22	120	80	1,275	36	Before operation
		-19	151	7.90	1.9	1.3	38	33	26	120	80	1,275	26	2 weeks after operation

## RESULTS

*Cardiac Output and Work*—In the patients without congestive failure the cardiac output before operation was within normal limits, whereas in the patients with congestive failure it was at or somewhat

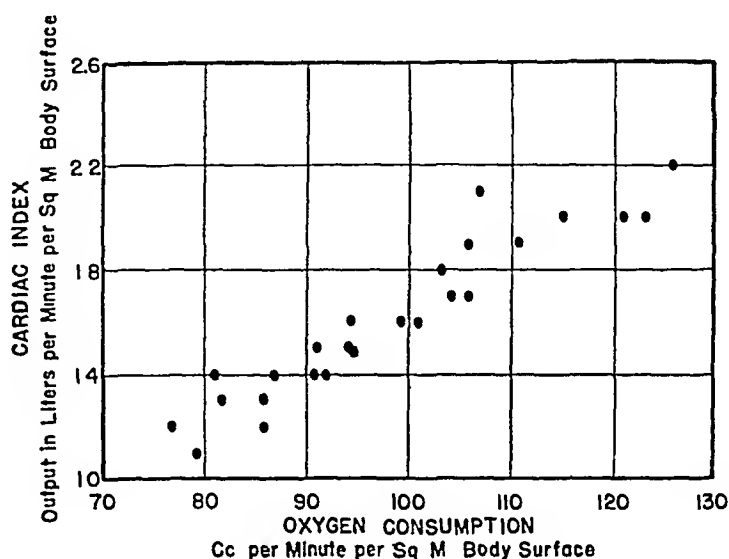


Fig 1—Relation between the oxygen consumption per square meter of body surface and the cardiac index in patients without congestive failure

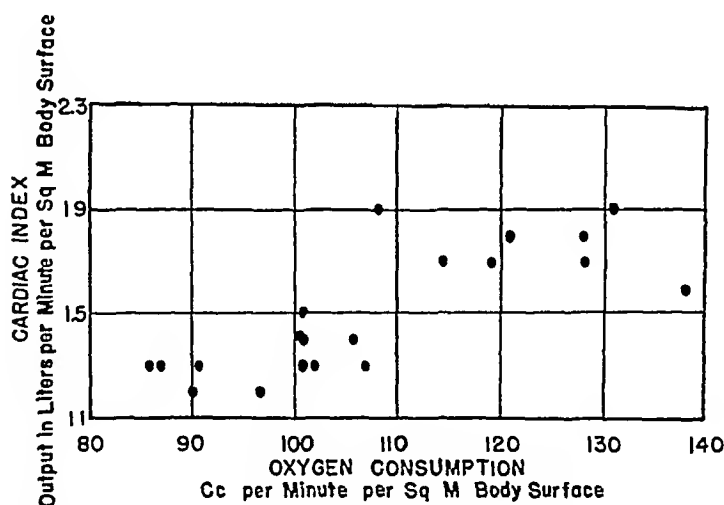


Fig 2—Relation between the oxygen consumption per square meter of body surface and the cardiac index in patients with congestive failure

below the lower limit of normal. After total thyroidectomy the cardiac output was decreased in all twenty-three patients (tables 1 and 2, charts 1 and 2). When the basal metabolic rates decreased to between minus 25 and minus 37 per cent, the cardiac indexes (cardiac output in liters per square meter of body surface) fell to between 1.1 and 1.4

(table 1, chart 1), as compared to the normal values of  $22 \pm 0.3$  <sup>10</sup> The output observed in cases 8, 9, 10, 11, 22 and 23 both before and after operation showed that as the basal metabolic rate falls the minute volume output of the heart decreases to a greater percental extent than does the oxygen consumption (table 3) The repeated measurements obtained in case 5, studied at various levels of basal metabolism after operation, also clearly exemplify this

The work of the heart was diminished after operation in every instance but one and generally paralleled the cardiac output In case 4 a slight increase in blood pressure occurred, which compensated for the fall in cardiac output, so that parallelism between the work of the heart and the decrease of metabolic rate was not close

*Arteriovenous Oxygen Difference*—An increase in arteriovenous oxygen difference was evident at low levels of metabolism (tables 1

TABLE 3—Percentage Decrease in Oxygen Consumption and Cardiac Output After Operation

Case	Decrease in Oxygen Consumption, Percentage	Decrease in Cardiac Output, Percentage
8	22.4	25.0
	34.7	45.0
	14.1	15.0
9	15.0	33.3
	12.2	28.6
10	14.6	15.0
11	19.8	27.3
22	9.2	10.5
	19.1	26.4
	26.0	36.8
23	15.7	26.8

and 2, charts 3 and 4) The disproportionate decrease in cardiac output noted (table 3) was associated with this progressive increase in arteriovenous oxygen difference Relatively minor changes in oxygen difference occurred when the basal metabolic rate had fallen to between minus 10 and minus 20 per cent At lower levels of metabolism these changes were much more striking (charts 3 and 4) These changes in arteriovenous oxygen differences were most clearly seen in patients without congestive failure In most cases the patients with congestive failure showed similar changes In one instance (case 20), however, in which a high arteriovenous oxygen difference was found preoperatively, there was a temporary decrease soon after operation, followed by an increase

*Velocity of Blood Flow*—In the patients without congestive failure the velocity of blood flow was usually decreased when hypothyroidism

<sup>10</sup> Grollman, A. Physiological Variations in the Cardiac Output of Man VI The Value of the Cardiac Output of the Normal Individual in the Basal Resting Condition, *Am J Physiol* 90:210, 1929

developed (table 1) In three of the twenty-three patients (cases 1, 4 and 11) the velocity of blood flow was not less than normal, although the cardiac output was strikingly decreased In two other patients (cases 5 and 6) the changes in circulation time and cardiac output were not in proportion In most instances, however, the changes in the velocity of

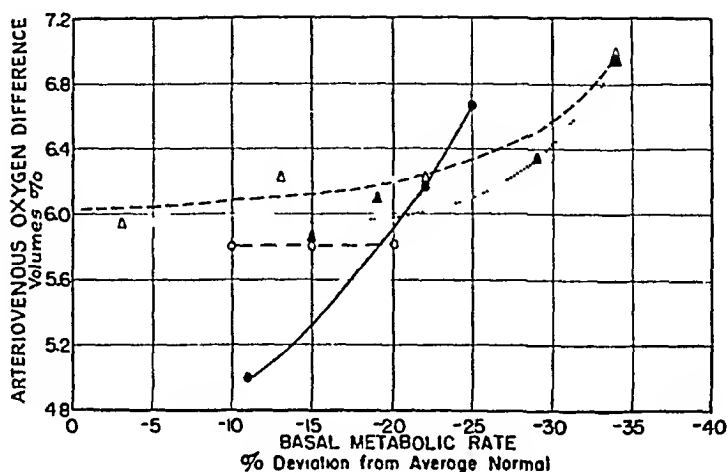


Fig 3—Relation between the arteriovenous oxygen difference and the basal metabolic rate in patients without congestive failure

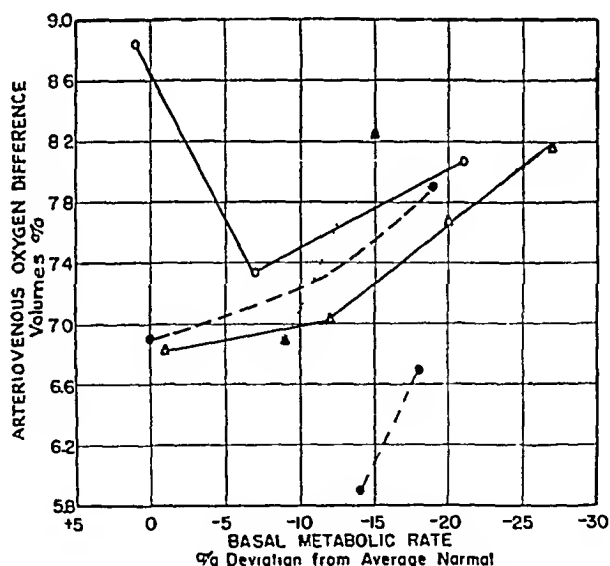


Fig 4—Relation between the arteriovenous oxygen difference and the basal metabolic rate in patients with congestive failure

blood flow and in the minute volume output roughly paralleled each other

The circulation time was very much increased in the patients with congestive failure even before operation (table 2) After operation the circulation time became still more slowed in ten instances, it was essentially unchanged in one case (case 20)

*Venous Pressure, Arterial Pressure and Vital Capacity*—The venous and arterial blood pressures and the vital capacity showed no significant changes after total thyroidectomy in the patients without cardiac decompensation (table 1). No striking changes in arterial blood pressure or in vital capacity were found after operation (table 2) in patients with congestive failure. The same was true of the venous pressure in most instances, in the one case (case 20) in which the venous pressure was slightly elevated before operation a decrease to within normal limits occurred postoperatively. In the other patients the venous pressure before operation was within normal limits, the patient having received prolonged medical treatment in order to achieve the most favorable physical condition possible preoperatively.

#### COMMENT

A high coefficient of correlation between the cardiac output and the basal oxygen consumption in normal persons has been demonstrated by Starr, Collins and Wood<sup>11</sup>. However, the studies of Bock and Field<sup>12</sup> on two patients with spontaneous myxedema showed that at low levels of metabolism the cardiac output is disproportionately decreased. The results of the present study demonstrate a similarity in this respect between spontaneous and induced hypothyroidism.

The disproportionate decrease in cardiac output observed by us in persons with hypothyroidism developing subsequent to total thyroidectomy is accompanied by an increase in arteriovenous oxygen difference. The latter increase first becomes evident when the basal metabolic rate has fallen to between minus 15 and minus 20 per cent and becomes progressively greater as the basal metabolic rate decreases below this level.

In one patient with congestive failure the arteriovenous oxygen difference was elevated before operation. This is a common finding in patients with congestive failure. In such patients the arteriovenous oxygen difference tends to return to normal as compensation is improved. In the patient just mentioned (case 20) a decrease in arteriovenous oxygen difference occurred shortly after operation, indicating an improvement in cardiovascular function. Subsequently the effect of the induced hypothyroidism became dominant and the arteriovenous oxygen difference increased.

The cause of the increased arteriovenous oxygen difference noted in hypothyroidism has not been determined. The increased arteriovenous difference is not to be regarded as evidence of heart failure due to

11 Starr, I, Jr, Collins, L. H., and Wood, F. C. Studies of the Basal Work and Output of the Heart in Clinical Conditions, *J. Clin. Investigation* **12** 13, 1933.

12 Bock and Field, cited by Means<sup>1</sup>.

"myxedema heart," since it occurred in patients with cardiac decompensation when the signs of congestive failure were disappearing instead of increasing (cases 20, 21 and 22). The fact that the venous pressure was not elevated in our patients with marked hypothyroidism is additional evidence that the circulatory changes were not due to cardiac decompensation. Estimation of the size of the heart on roentgen examination in fifteen of the patients before and after operation, furthermore, revealed enlargement after the development of hypothyroidism in only five, while in two of the patients with congestive failure (cases 12 and 15) the size of the heart actually decreased. The significance of such changes has been discussed elsewhere<sup>13</sup>

It is of interest that in patients with hypothyroidism there is an increase in arteriovenous oxygen difference, while in patients with an elevation of the metabolic rate due to exophthalmic goiter the oxygen difference is usually decreased,<sup>14</sup> since the cardiac output is increased more than the oxygen consumption. It has been suggested<sup>14e</sup> that the changes in the cardiac output and the oxygen difference which occur in exophthalmic goiter are related in some way to the presence of increased amounts of thyroid hormone in the blood stream. However, in one of our patients (case 11), with hyperthyroidism but with a normal basal metabolic rate, a normal arteriovenous oxygen difference was found, this suggests that the arteriovenous difference is related to the level of metabolism rather than to the degree of activity of the thyroid gland. The changes in arteriovenous oxygen difference observed in patients with disorders of metabolism may be considered as manifestations of vasomotor readjustments which are designed to maintain a normal internal body temperature, the decreased arteriovenous oxygen difference associated with the elevation of metabolism usually found in exophthalmic goiter being due to an abnormally rapid flow of blood to the lungs and skin in an attempt to throw off the excessive heat produced in this condition. Conversely, the increased oxygen difference of hypothyroidism may be an attempt to conserve heat.

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13 Davis, D., Weinstein, A. A., Riseman, J. E. F., and Blumgart, H. L. Treatment of Chronic Heart Disease by Total Ablation of the Thyroid Gland. VII. The Heart in Artificial Myxedema, *Am Heart J* **10** 17, 1934.

14 (a) Liljestrand, G., and Stenstrom, N. Clinical Studies on the Work of the Heart During Rest. I. Blood Flow and Blood Pressure in Exophthalmic Goiter, *Acta med Scandinav* **63** 99, 1925. (b) Robinson, G. C. The Measurement of the Cardiac Output in Man and Its Variations, *J A M A* **87** 314 (July 31) 1926. (c) Lauter, S. Ueber den Kreislauf bei Basedow, *Verhandl d deutsch Gesellsch f inn Med* **40** 292, 1928. (d) Fullerton, C. W., and Harrop, G. A. The Cardiac Output in Hyperthyroidism, *Bull Johns Hopkins Hosp* **46** 203, 1930. (e) Boothby, W. M., and Rynearson, E. H. Increase in Circulation Rate Produced by Exophthalmic Goiter Compared with That Produced in Normal Subjects by Work, *Arch Int Med* **55** 547 (April) 1935. Means<sup>1a</sup> Bansi and Groscurth<sup>1e</sup>

Calculations from the data obtained in the present study show that the work of the left ventricle diminishes as the basal metabolic rate decreases after total thyroidectomy. At levels of metabolism below minus 15 to minus 20 per cent, the work of the heart is reduced more than the oxygen consumption, a reduction of 30 per cent in the oxygen consumption being associated with a decrease of 40 per cent in the cardiac work. In every patient studied before and after operation the reduction in the work of the heart was associated with clinical improvement. Blumgart and his co-workers<sup>2</sup> have advanced the concept that the relief obtained in congestive failure and in angina pectoris after total thyroidectomy is due to lessened demands on the heart resulting from the decreased oxygen consumption in hypothyroidism. Our observations support this concept and show, moreover, that the diminution in the work of the heart at low levels of metabolism even exceeds the reduction in oxygen consumption.

In patients operated on for angina pectoris, relief is due to reduction of the work of the heart to or below an amount which it can do without the development of anoxemia. Diminution of the output of the left ventricle does not affect the coronary blood flow appreciably,<sup>15</sup> so the nutrition of the myocardium is not impaired by the reduction of cardiac output which follows total thyroidectomy.

In the patients with congestive failure the lowest basal cardiac index observed before operation was 1.6 (table 2). After total thyroidectomy, when the basal metabolism had decreased to hypothyroid levels, the cardiac index was reduced to between 1.2 and 1.4 in all cases (table 2). Thus, in patients with congestive failure the basal oxygen consumption after total thyroidectomy falls well below the point at which it merely balances the low cardiac output and the cardiac output at rest coincidentally becomes reduced below the preoperative level. This makes it possible for the cardiac output in such patients to increase appreciably in response to work, so that the degree of activity may be increased without discomfort. In addition, a significant measure of rest is afforded the heart in the patients with angina pectoris as well as in those with congestive failure as a result of the marked diminution in basal cardiac work which occurs after operation.

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<sup>15</sup> Anrep, G. V., and Segall, H. N. Regulation of the Coronary Circulation, *Heart* **13** 239, 1926. Anrep, G. V., and Hausler, H. The Coronary Circulation. I. The Effect of Changes of the Blood Pressure and of the Output of the Heart, *J. Physiol.* **65** 357, 1928. Anrep, G. V., Davis, J. C., and Volhard, E. The Effect of Pulse Pressure upon the Coronary Blood Flow, *J. Physiol.* **73** 405, 1931. Rein, H. Die Physiologie der Herz-Kranzgefäße. I. Mitteilung, *Ztschr. f. Biol.* **92** 101, 1932. Anrep, G. V., and Saalfeld, E. F. The Effect of the Cardiac Contraction upon the Coronary Flow, *J. Physiol.* **79** 317, 1933.



## SUMMARY AND CONCLUSIONS

Data on the changes in the cardiac output and related aspects of the circulation after total thyroidectomy in twenty-three patients are presented

The output in volume per minute and the work of the heart are greatly diminished in hypothyroidism following total ablation of the normal thyroid gland

The cardiac output decreases progressively to a greater extent than the oxygen consumption as the basal metabolic rate falls in hypothyroidism. This disproportionate decrease in cardiac output is accompanied by a progressive increase in the arteriovenous difference. These changes are most striking when the basal metabolic rate has fallen below minus 15 to minus 20 per cent.

In nineteen of twenty-three patients the velocity of blood flow was slowed when the cardiac output was low. In patients with congestive failure the velocity of blood flow was much slower than in those without congestive failure. In three instances the velocity of blood flow did not reflect accurately the work of the heart.

The venous pressure, arterial pressure and vital capacity were not significantly altered after total thyroidectomy in the patients in this series.

The measurements obtained for the same patients by the acetylene and ethyl iodide methods are compared. The results are the same by the two methods under the conditions of the experiments described.

Reduction in the work of the heart was associated with clinical improvement in the patients studied.

The data obtained in this study are in harmony with the concept that the relief obtained after operation in patients with angina pectoris is due principally to reduction of the work of the heart to or below an amount which it can do without the development of anoxemia.

In patients with congestive failure the basal oxygen consumption after total thyroidectomy falls well below the point at which it merely balances the low cardiac output, and the cardiac output at rest coincidentally becomes reduced below the preoperative level. This makes it possible for the cardiac output in such patients to increase appreciably in response to work, so that the degree of activity may be increased without discomfort.

In addition, the marked diminution in basal cardiac work which occurs in all patients after operation affords the heart a significant measure of rest.

# LIVER THERAPY FOR COMBINED SCLEROSIS

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AND

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The experimental work of Whipple and his associates on anemia, leading to the clinical application of liver therapy by Minot and Murphy in 1926, is one of the brilliant chapters of achievement in American medicine. Owing to these researches physicians are now able better to understand and control the disease of the blood classified as pernicious anemia. One of the serious complications of this condition is a degenerative process of the spinal cord designated as combined sclerosis because of the pathologic areas of gliosis resulting from degenerative processes in the most involved portions of the cord, the posterior and lateral fiber tracts. A far better nomenclature for this disease is subacute myelomic degeneration, for the fibers in the brain may also be involved, and there is evidence of involvement of the myelin sheaths of the peripheral nerves as well.

The neural complications may be present without appreciable anemia and may not be present with a high degree of anemia, while they are rarely seen with secondary anemia. The neural degenerations cannot, therefore, logically be attributed to the anemia itself. The prevailing theory is that there is a deficiency factor in pernicious anemia which determines the blood picture and the neural degenerations and which may be emphasized in the blood, in the nervous system or in both. This deficiency has been designated as a lack of the antianemic liver fraction G of Cohn, which is absent from the livers of patients with pernicious anemia not treated with liver.

The clinical and pathologic manifestations of subacute myelomic degeneration were described in a paper<sup>1</sup> read before the Section of Neuropsychiatry of the State Medical Society in 1917, in a report of 23 cases with 4 necropsies, and since then little has been added to the knowledge of the physical characters of this disorder. It is a relatively frequent

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Read before the Section of Neuropsychiatry at the Sixty-Fourth Annual Session of the California Medical Association, Yosemite National Park, Calif., May 15, 1935

1 Schaller, W F. Spinal Cord Changes in Combined Sclerosis, California State J Med **16**:44 (Jan) 1918

neurologic condition, statistics showing an incidence approximately four times that of multiple sclerosis. Before the introduction of liver therapy efforts to combat neural complications were discouraging in the extreme, and the disease invariably progressed, since liver therapy was introduced, in our experience there has been a dramatic change in response to treatment. Reports on the results of liver therapy in patients with neurologic complications of pernicious anemia have been variable, favorable publications are notably those of Minot and Murphy,<sup>2</sup> Bubert,<sup>3</sup> Mason,<sup>4</sup> Davidson, McCrie and Gullard,<sup>5</sup> Fried,<sup>6</sup> Richardson,<sup>7</sup> Ungley and Suzman,<sup>8</sup> Lottig,<sup>9</sup> Farquharson and Graham,<sup>10</sup> Schilling,<sup>11</sup> Starr,<sup>12</sup> Strauss and Castle,<sup>13</sup> Baker, Bordley and Longcope<sup>14</sup> and Meulengracht<sup>15</sup>

Bubert reported a case in which there was a steady downward course before the institution of liver therapy in 1926, liver therapy and the maintenance of a sustained red blood cell count of over 5,000,000 for nine months resulted in a marked improvement in the neurologic status. Richardson emphasized the necessity of keeping the red blood cell count above 4,500,000 in order to prevent involvement of the nervous system.

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4 Mason, E. H. Pernicious Anemia, *J. A. M. A.* **90** 1527 (May 12) 1928.

5 Davidson, G., McCrie, J. G., and Gullard, G. L. The Treatment of Pernicious Anemia. Liver Diet, *Lancet* **1** 847, 1928.

6 Fried, B. M. Subacute Combined Degeneration of the Spinal Cord in Pernicious Anemia, *J. A. M. A.* **92** 1260 (April 13) 1929.

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14 Baker, B. M., Bordley, J., and Longcope, W. T. The Effect of Liver Therapy on the Neurologic Manifestations of Pernicious Anemia, *Am. J. M. Sc.* **184** 1, 1932.

15 Meulengracht, E. Verhütung und Behandlung der Rückenmarksstörungen bei perniziöser Anämie, *Klin. Wchnschr.* **12** 1163 (July 29) 1933.

In Starr's patients whose red blood cell count was kept above 5,000,000 progressive degeneration of the nervous system did not occur. Baker, Bordley and Longcope stated that although the correlation between improvement in the neurologic status and the blood picture is not absolute, it is noticeable that patients showing marked improvement usually have a high red cell count. Improvement in 58.93 per cent of signs and symptoms was found in their patients who were treated for more than ten months. A number of patients were given 10 pounds (4.5 Kg.) of liver weekly (650 Gm. daily or its equivalent in powdered extract). The necessity for long continued intensive treatment is emphasized. There has recently appeared a significant article by Strauss and his co-workers<sup>16</sup> concerned only with changes referable to the spinal cord in patients observed for an average period of three years. Twenty-six patients were selected who had spasticity, ataxia or both, resulting in definite disturbances of locomotion signifying at least moderately severe degeneration in the cord. Eight of these patients showed unfavorable progress during oral administration of liver in amounts possible for them to ingest but responded favorably to parenteral administration of liver preparations equivalent in hematopoietic effectiveness to still greater quantities of orally administered material. The authors therefore emphasized the greater effectiveness of parenteral treatment, attributed to larger equivalent amounts than may be given orally, and called attention to the fact that patients receiving oral treatment should be carefully observed for the development of symptoms or signs relative to the nervous system. Patients with distinct neurologic lesions should be given parenteral therapy at once. In their study the "initial status" was evaluated only after the red blood cells numbered 3,500,000 per cubic millimeter. The average count was 4,300,000, and in the final neurologic status the count was 4,780,000. In the series 58 per cent of all abnormal signs encountered in the 26 patients remained unchanged, 17 per cent disappeared, and 25 per cent were improved. Treatment for all patients consisted of the intramuscular injection of solution of liver extract<sup>17</sup> in a minimum dose of 10 cc. once every three weeks. In commencing treatment of a previously untreated patient the usual procedure was to inject 10 cc. of the extract every three or four days during the first two to three weeks and then to give weekly injections of the same amount for the remainder of the first year. The dose was equivalent to about 50 per cent more than the amount taken by mouth by many patients. Strauss and his co-workers expressed the belief that

16 Strauss, M. B., Solomon, P., Schneider, A. J., and Patek, A. J. Subacute Combined Degeneration of the Spinal Cord in Pernicious Anemia, *J. A. M. A.* **104** 1587 (May 4) 1935.

17 Liver extract-Lilly (N. N. R.) was used for oral administration, and solution of liver extract-Lilly (N. N. R.), for intramuscular administration.

disagreement in the literature often arises from the fact that results were recorded over too brief periods for adequate treatment to demonstrate its full effect

The foregoing writers, therefore, stressed the importance of a high red cell count and of its maintenance over a considerable period

Some writers have either doubted or denied a specific action of liver therapy against neurologic complications. We shall briefly review and analyze these adverse reports

#### DISSENTING OBSERVATIONS ON BENEFICIAL EFFECTS OF LIVER THERAPY IN CONTROLLING NEURAL MANIFESTATIONS

The earliest adverse reports, notably those of Sturgis, Isaacs and Smith,<sup>18</sup> Cohen,<sup>19</sup> McAlpine,<sup>20</sup> Seyderhelm,<sup>21</sup> Curschmann,<sup>22</sup> Krause,<sup>23</sup> and Carey,<sup>24</sup> represent conclusions based on the lack of either adequate treatment from the point of view of the blood picture or the maintenance of a normal blood picture for a reasonable length of time. Sturgis and his co-workers used powdered liver extract, they reported 28 cases in 1927. The equivalent of 1 pound (453 Gm) of liver was given daily, and in some cases as much as 1½ pound (680 Gm) of liver was given, this was reduced to ½ pound (227 Gm) when a convincing rise in the number of red blood cells had occurred. They stated that improvement in signs and symptoms does not parallel the improved blood pictures. The red blood cell counts were relatively high in the cases they reported, but the longest periods of treatment reported were one hundred and seventeen and one hundred and three days, respectively. It is apparent from later experience that adequate doses were not maintained for a sufficient period to justify the formulation of a definite opinion as to course and prognosis.

Smithburn and Zervas<sup>25</sup> in 1931 reported on a group of 35 patients showing neurologic involvement in a total series of 115 patients with

18 Sturgis, C. C., Isaacs, R., and Smith, M. The Treatment of Pernicious Anemia with Liver Extract, *Ann Int Med* **1** 994, 1927

19 Cohen, A. E. Subacute Combined Sclerosis, Progressive During Remission of Pernicious Anemia, *J A M A* **90** 1787 (June 2) 1928

20 McAlpine, Douglas. A Review of the Nervous and Mental Aspects of Pernicious Anemia, *Lancet* **2** 643 (Sept 28) 1929

21 Seyderhelm, R. Möglichkeiten und Grenzen der Lebertherapie, *Deutsche med Wchnschr* **55** 1704 (Oct 11) 1929

22 Curschmann, Hans. Die Nervenstörungen der Biermerschen Anämie und die Lebertherapie, *Med Klin* **25** 1767 (Nov 15) 1929

23 Krause, F. Ueber das Versagen der Lebertherapie bei den funikulären Erkrankungen der perniziösen Anämie, *Klin Wchnschr* **8** 2177 (Nov 19) 1929

24 Carey, J. B. Pernicious Anemia with Fatal Termination During a Liver Diet, *Arch Int Med* **47** 893 (June) 1931

25 Smithburn, K. C., and Zervas, L. A. Neural Symptoms and signs in Pernicious Anemia, *Arch Neurol & Psychiat* **25** 1100 (May) 1931

pernicious anemia They administered fractions of liver deemed adequate to maintain what they designate a normal blood level Three of the 35 cases were detailed by the authors In case 1 the highest red cell count mentioned was 4,300,000, in case 2, in which the disease was reported to progress while treatment was given, the erythrocyte count at no time reached 4,000,000, and in case 3 the only mention of results of treatment was that the blood count returned to "normal" Smithburn and Zerfas' conclusions were that neurologic changes may develop or steadily progress while the patient is receiving daily amounts of liver adequate to maintain a normal erythrocyte level This report obviously cannot be seriously considered as one dealing with a group of patients adequately treated by therapy controlling the erythrocyte count

Carey stated that by adequate "is meant an amount found in other patients so treated that will keep the blood count and hemoglobin up to reasonable normal levels" The highest count in any of his patients is reported as 3,850,000 Of Sargent's<sup>26</sup> 4 patients, the only one who had a normal blood count was objectively improved Ahrens,<sup>27</sup> without choosing to draw conclusions as to the efficacy of liver, stated that the maintenance of a high hemoglobin content and a red cell count of 5,000,000 does not prevent or improve changes in the cord, and he called attention to 3 cases in his series as proof of this contention, however, a review of these cases is not convincing, as regards either the maintenance of the blood picture or the duration of treatment Fahr<sup>28</sup> made necropsies on 13 patients with pernicious anemia treated with liver in whom degeneration in the cord was found He spoke of a hypothetic toxic condition determining organic changes independent of the condition of the blood Davison<sup>29</sup> reported on 7 necropsies of patients treated with liver and compared the pathologic observations with those on untreated patients He stated "Histopathologically, all the treated patients showed progressive or glial changes (gliosis) These changes were not observed in the untreated patients with subacute combined degeneration The myelin sheaths and axis cylinders were not influenced by the liver therapy" The gliosis might well be considered a reparative process not found in untreated patients

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26 Sargent, W Treatment of Subacute Combined Degeneration of the Cord by Massive Iron Dosage, *Lancet* **1** 230 (Jan 30) 1932

27 Ahrens, R S Neurologic Aspects of Primary Anemia, *Arch Neurol & Psychiat* **28** 92 (July) 1932

28 Fahr, T Pathologisch-anatomische Beitrage zur Kritik der Lebertherapie bei der perniziösen Anämie, *Deutsche med Wchnschr* **57** 8 (Jan 2) 1931

29 Davison, C Subacute Combined Degeneration of the Cord Changes Following Liver Therapy, a Histopathologic Study, *Arch Neurol & Psychiat* **26** 1195 (Dec) 1931

Grinker and Kandel<sup>30</sup> concluded that liver therapy is not efficacious in improving or preventing degeneration in the central nervous system complicating pernicious anemia and that in the majority of cases the disease progresses slowly, no matter what therapy is employed. They made the pertinent observation that changes in neurologic signs may be falsely interpreted and that weakness may imitate damage in the cord. They further made the excellent point that well controlled neurologic observations are essential to an evaluation of the actual neural status during treatment. They studied a series of 50 patients over a period of two and a half years and defined adequate treatment as a quantity of liver sufficient to maintain a normal blood level, associated with the feeling of well-being peculiar to health. Their dose averaged the equivalent of 1 pound (453 Gm) of liver a day in the form of domestic extract. The results in 37 patients who received treatment were analyzed. In 19 there was no change in neurologic status, in 10 the condition progressed under therapy, 4 showed apparent improvement, and 4 showed definite improvement. Two patients in the series received liver parenterally. In only 5 did the stated blood count attain normal accepted standards. In 1 patient (case 30) lost inferior tendon reflexes returned during the period of treatment, whereas other neurologic signs remained the same, the failure of deep sensation to return was interpreted as progression of the involvement in the lateral tracts, in 1 patient (case 29) inferior tendon reflexes were lost during the period of treatment.

Goldhamer and his co-workers<sup>31</sup> reported a high incidence (89.2 per cent) of involvement of the nervous system in a series of 461 patients with pernicious anemia. A level of 4,000,000 red cells was considered as an index of reasonable treatment. Of the patients who received adequate treatment, in 2 per cent the signs referable to the spinal cord were improved, in 83 per cent they were unimproved, and in 15 per cent they were aggravated. Of those who received inadequate treatment, improvement of signs referable to the cord occurred in 2 per cent, no improvement was noted in 59 per cent, and the signs became worse in 39 per cent. Improvement in symptoms was observed in less than 50 per cent of the patients. Goldhamer and his co-workers concluded that antianemic therapy does not have a specific curative effect on degeneration in the spinal cord but contributes only indirectly to improvement in the manifestations referable to such degeneration.

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30 Grinker, R. R., and Kandel, E. Pernicious Anemia. Results of Treatment of the Neurologic Complications, *Arch Int Med* 54: 831 (Dec) 1934.

31 Goldhamer, S. M., Bethell, F. H., Isaacs, R., and Sturgis, C. C. The Occurrence and Treatment of Neurologic Changes in Pernicious Anemia, *J A M A* 103: 1663 (Dec 1) 1934.

## ADEQUATE THERAPY

Adequate therapy may be defined as the kind and amount of administration of a given remedy required to achieve a desired result with a strict control of the potency of the preparation and the regularity of its administration. Any physician who has had extensive experience with oral liver therapy cannot but be impressed with the difficulty of keeping patients to the faithful observance of prescribed dosage, by reason of the distaste and ennui incidental to ingestion of large amounts of liver. Because of this practical objection, liver extract was prepared in powdered form, and in 1931 a soluble extract became available for parenteral administration. These preparations have been standardized to correspond with whole liver, of which 225 Gm daily has been estimated as the average maintenance dose in cases of pernicious anemia. When the central nervous system is involved one is faced with a situation comparable to that in cases of neurosyphilis, in which protracted and specialized forms of treatment and, as a rule, dosage far in excess of that required in systemic syphilis are required. Oral administration of liver may not be wholly effective or may be impracticable. Parenteral injections of higher potency have been available only in the recent past. Another important consideration of an adequate therapy is the response of the blood. There is frequent reference in the literature to blood values deemed as satisfactory responses to therapy which are far below normal standards. Williamson<sup>32</sup> designated the following numbers of red cells as normal for adults between the ages of 21 and 70 years: males, 5,180,000, females, 4,800,000. It is not solely a rational procedure but a responsible obligation on the part of the physician to endeavor to attain a normal red cell count and a high hemoglobin content, in fact, the level for both should be higher than normal in order to provide an overcompensatory effect in cases in which the condition is refractory. A strict observance of this requirement was emphasized in the discussion on this subject at the session of the American Medical Association in Milwaukee in 1933 before the Section on Nervous and Mental Disease by William P. Murphy. A recent personal communication from this high authority is to the effect that "if the blood is maintained at a normal level, neurologic changes do not start, they do not progress, and they are improved in 100 per cent of instances."

As our experience and convictions are at variance with those of writers who have disclaimed a specific action on the neural complications of pernicious anemia, we have recently reviewed our records of instances of neurologic complications in cases of this disease and have

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32 Williamson, C. S. Influence of Age and Sex on Hemoglobin, *Arch. Int. Med.* **18** 505 (Oct.) 1916.



selected 1931 as the date from which more effective preparations were available for treatment. Forty cases were reviewed. It was at once apparent that in only a small number of cases in this series were there fulfilled the requirements of a sustained, adequate therapy under control of the blood picture and neurologic status. It is to be emphasized, in accord with Grinker's statement, that the neurologic record should be considered of equal importance with the blood picture. Each blood count should be checked by a neurologic examination—subject to a double check, as it were.

#### REPORT OF CASES

The patients are divided in two groups. The first group includes patients adequately treated for an appreciable period of time and having a normal blood count (Williamson), the second group includes patients observed for considerable periods of time receiving therapy not fully conforming to the standard of sustained, controlled, adequate treatment but showing a satisfactory neurologic status and occupational activity.

*Group 1*—This group comprises 5 cases.

**CASE 1** (Observed for SIX Years)—A 67 year old retired insurance man was seen in the medical clinic on Feb 18, 1929, he complained of constipation, gas and anorexia. Physical examination gave normal results except for papillary atrophy of the tongue and some loss of vibratory sensation in the lower extremities. Laboratory examination showed a lack of free hydrochloric acid in the gastric contents, a red cell count of 2,400,000, 60 per cent hemoglobin, a color index of 1.25 and moderate poikilocytosis and anisocytosis. A diagnosis of pernicious anemia was made, and the patient was instructed to eat 225 Gm of whole liver daily. By May 3, 1929, his red cell count had risen to 4,000,000 and his hemoglobin content to 78 per cent, and there was a great increase in his feeling of well-being. He complained of the amount of liver he was required to eat, and on Oct 7, 1929, the treatment was changed to two vials of liver extract<sup>17</sup> daily. This regimen maintained his red cell count at approximately 4,000,000 until Oct 30, 1930, when he first complained of numbness in the hands and legs. Examination at this time by Dr. Henry Newman gave the following results: Romberg sign, positive, coordination in the arms, poor, deep reflexes, equal and active, pyramidal tract reflexes, present, and vibratory sensation, impaired below the waist and almost absent below the knees. The patient was hospitalized and received ten hyperpyrexia baths. The dose of liver was increased to three vials of liver extract<sup>17</sup> and  $\frac{1}{4}$  pound (113 Gm) of whole liver daily. He also received injections of nonspecific protein. In spite of this treatment, which maintained his red cell count at an average of 4,000,000, he complained of progressive weakness, and in December 1931 was again hospitalized. His blood count showed 3,650,000 red cells and 79 per cent hemoglobin. Reexamination by Doctor Newman showed inability to walk without assistance, spastic and ataxic gait, incoordination of the arms and legs, equal deep reflexes, positive Babinski, Gordon and Oppenheim signs bilaterally, patellar clonus, and further diminution of vibratory sensation. He was given twenty-four vials of liver extract<sup>17</sup> by stomach tube, but no reticulocyte response occurred in nine days. After this he received eight intramuscular injections of solution of liver extract<sup>17</sup> of 10 cc each. He was dismissed to the clinic,

where he received injections of 8 cc of liver extract three times a week. By Feb 15, 1932, his red cell count was 4,700,000 and his hemoglobin content 89 per cent, he felt much improved and was able to attend the clinic by himself. On March 9, 1932, his red cell count was 5,000,000 and his hemoglobin content 84 per cent, and under the aforementioned regimen the blood picture was maintained close to that level. On Feb 20, 1933, he entered the hospital for a check-up. His red cell count was 5,100,000 and his hemoglobin content 95 per cent. Examination by the house physician showed slightly spastic and ataxic gait, active and equal deep reflexes, absence of signs referable to the pyramidal tract and a questionable Romberg sign. The patient continued to receive treatment in the clinic as before, and on July 20, 1934, the dose of liver extract was reduced to 10 cc administered intramuscularly twice weekly. He complained, however, of not feeling up to par, and on Sept 18, 1934, his red cell count had fallen to 3,980,000. He was therefore

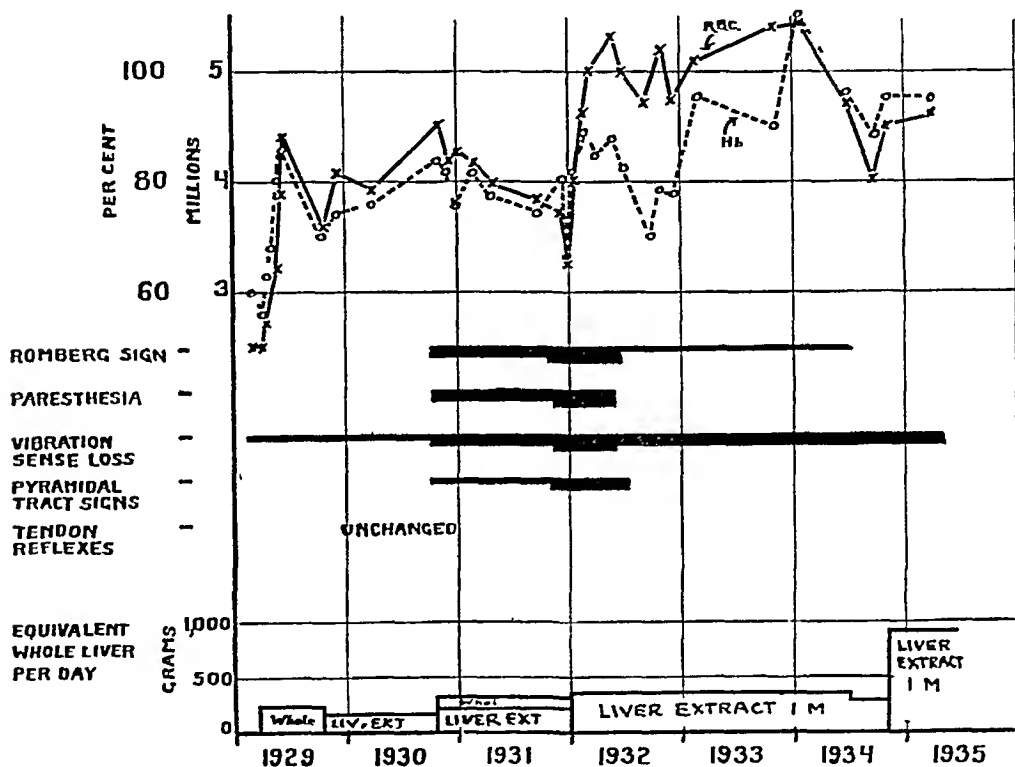


Fig 1 (case 1)—Graphic representation of results of liver therapy. From 1929 to 1931, inclusively, the patient received liver extract<sup>17</sup> orally, from 1932 to October 1934 he received liver extract<sup>17</sup> intramuscularly, and during the remaining period of treatment, concentrated solution of liver extract<sup>33</sup> intramuscularly.

given 10 cc of liver extract intramuscularly three times weekly, and on October 26 his count had risen to 4,500,000. At this time treatment was changed to intramuscular injections of 5 cc of concentrated solution of liver extract<sup>33</sup> twice weekly. On March 12, 1935, his red cell count was 4,530,000 and his hemoglobin content 87 per cent. Examination by Doctor Newman showed normal gait, a negative Romberg sign, good coordination, active and equal reflexes, absence of clonus and of pyramidal tract signs and diminution but not absence of vibratory sensation in the legs.

<sup>33</sup> Solution of liver extract concentrated-Lilly (N N R) was used.

CASE 2 (Observed for Two Years) —An American dressmaker, aged 52, was hospitalized on March 10, 1933, she presented a neurologic condition of dysesthesias, impairment in vibratory sensation below the knees, unsteady gait, active reflexes throughout without pathologic signs referable to the pyramidal tract and a negative Romberg sign. The red cell count was 2,500,000 and the hemoglobin content 60 per cent. There was no free hydrochloric acid in the stomach contents. The patient was given 10 cc of solution of liver extract<sup>17</sup> intramuscularly for seven consecutive days and thereafter three weekly injections of the same amount of that preparation until December 1933, when the dosage was reduced to weekly injections, which were continued throughout 1934. Then 3 cc of a solution of liver extract<sup>34</sup> was injected weekly. In March, April and May of 1934 there was a complicating diarrhea which followed ingestion of liver and bacon. In August the medication was supplemented by three capsules of extralin daily. On

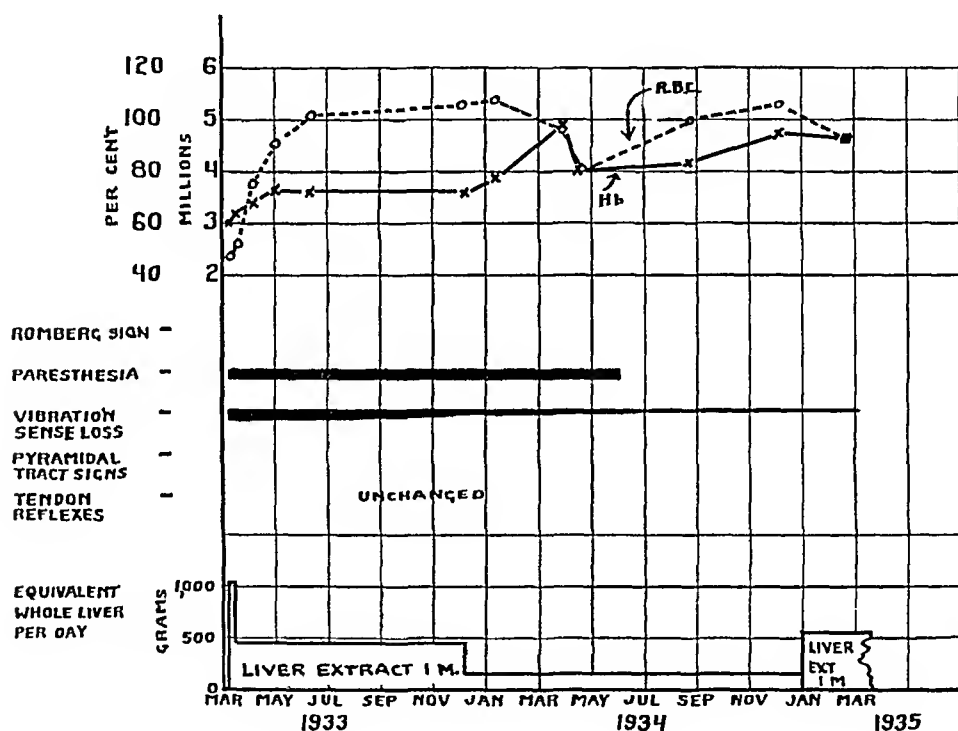


Fig 2 (case 2) —Graphic representation of results of liver therapy. From March 1933 to January 1935 the patient received liver extract,<sup>17</sup> and from January to March 1935, another preparation<sup>34</sup> of liver extract.

June 16, 1933, the blood count showed 5,100,000 red cells and 72 per cent hemoglobin, it rose to 5,400,000 red cells and 78 per cent hemoglobin in January 1934. In April it fell to a low level of 4,000,000 red cells and 80 per cent hemoglobin at the period of the gastro-intestinal upset. In September 1934 the red blood cell count rose to 5,000,000 and the hemoglobin content to 84 per cent, and in December the level reached 5,280,000 and 95 per cent, respectively. The last examination of the blood, in February 1935, showed 4,530,000 red cells and 92 per cent hemoglobin. In May 1933 vibratory sensation was improved in both legs,

34 Lederle solution of liver extract parenteral refined and concentrated (N N R) was used.

in April 1934 Doctor Bloomfield stated, "There is still some impairment of vibratory sensation, but the function seems to be better than a year ago" In March 1935 vibratory sensation was not diminished The negative signs remained so and the tendon reflexes were unchanged In June 1934 the patient still complained of slight numbness in the extremities and of unsteadiness

CASE 3 (Observed for Thirteen Months) —An American housewife, aged 49, entered the Lane Hospital in August 1932, complaining of numbness of the hands and feet which had been present for eleven months Examination showed a positive Romberg sign, unsteady gait, hyperactive knee and ankle jerks, a positive Babinski sign bilaterally and absence of vibratory sensation from the iliac crests down The red blood cells numbered 2,900,000, and the hemoglobin content was 74 per cent Analysis of the gastric contents showed no free hydrochloric acid

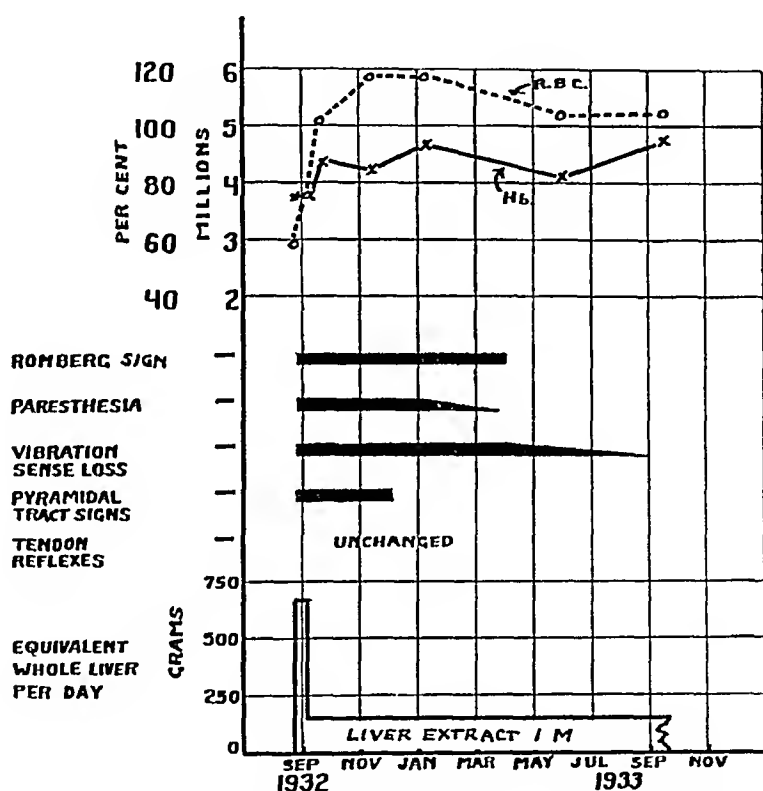


Fig 3 (case 3) —Graphic representation of results of liver therapy The patient received liver extract<sup>17</sup>

Therapy was started by intensive intramuscular injections of solution of liver extract,<sup>17</sup> 90 cc was administered over a period of fourteen days, producing a prompt reticulocyte response and an increase of 1,000,000 red cells Thereafter the dose was reduced to 10 cc weekly In September 1932 the red cells numbered 5,100,000 and the hemoglobin content was 87 per cent, in November the red cell count was 5,900,000 and the hemoglobin content 84 per cent In December 1932 examination by Dr Henry Gibbons gave the following results vibratory sensation, present at ankles but very faint, Babinski sign, negative, Romberg sign, 2 plus, gait, slightly unsteady In January 1933 the red cells numbered 5,900,000 and the hemoglobin content was 93 per cent In April 1933 Doctor Gibbons issued the following report "The Romberg sign is negative and the patient feels remarkably well" In June 1933 there were 5,200,000 red cells and 81 per cent hemoglobin In September 1933 Doctor Gibbons stated "The Romberg sign is negative, coor-

dination is normal, the inferior tendon reflexes are hyperactive, the Babinski sign is negative, and vibratory sensation is normal" The red blood cells numbered 5,200,000, and the hemoglobin content was 95 per cent

CASE 4 (Observed for Four Years) —A physician from another state, aged 60, consulted one of us in April 1931. He complained of bodily and mental fatigue, diminished manual dexterity and coordination in his surgical work and a mental feeling of indecision, which resulted in his temporarily discontinuing his professional work. His blood picture was of pernicious type and showed 3,500,000 red cells and 65 per cent hemoglobin. Repeated analyses of the gastric contents revealed an absence of free hydrochloric acid. Examination showed diminution of knee jerks and absence of ankle jerks, dorsiflexion responses of the great toes, diminution of vibratory sensation at the ankles, particularly over the left ankle. There was a slight Romberg sign and ataxia of all the extremities. In September 1931 the patient wrote "A mental haze and confusion which had been present for a number of years disappeared, and there has been a marked recession in the numbness and stiffness of my fingers and feet. I am using desiccated stomach (ventriculin) at the present time, with apparently good results. My last blood count after a month of maintenance dose showed 5,600,000 red cells and 97 per cent hemoglobin." In April 1935 he wrote that an examination of the blood showed a red cell count of 4,900,000 and 83 per cent hemoglobin, that his general condition had been good in the interval, that he was much stronger physically and was better coordinated and that there was no evidence of material advance in the neural spinal involvement. The inferior tendon reflexes were unchanged, except that the left ankle jerk had returned, the Romberg sign was negative, and the plantar reflex was in flexion. Vibratory sensation was described as "unsatisfactory as to legs, apparently lost." This patient was first given liver extract,<sup>17</sup> later desiccated stomach, U S P, was used, and at the time of writing he states that intramuscular injections are much more efficient than oral ingestion of liver. This patient showed improvement in the following neurologic signs: return of one ankle jerk, a negative Romberg sign, better coordination, and reversal of the Babinski sign. From the analysis of signs, according to Grinker, further loss of vibration is questionable because of return of deep reflexes in the absence of signs referable to the pyramidal tract.

CASE 5 (Observed for Eight Years) —In 1926 a physician, aged 50, was examined by Dr. Alfred C. Reed and Dr. Joseph Catton of San Francisco because of gastro-intestinal disturbances which had existed for five years—the disorder being described by Doctor Reed as "spruelike" symptoms—and also because of dysesthesias, hypesthesias in all extremities, insecurity of balance and awkwardness of finger movements, which started later with the oncoming of anemia. Physical examination showed a moderate enlargement of the spleen, irregular, low grade fever and a low grade chronic ethmoid infection. The results of laboratory examinations were as follows: Eight or nine specimens of stool showed no parasites, abnormal constituents or excess of fat. The gastric analysis demonstrated absence of free hydrochloric acid. The blood showed 2,600,000 red cells, 60 per cent hemoglobin (Sahli), a color index of 1.15 and 4,725 white cells, with 56 per cent polymorphonuclears and 44 per cent lymphocytes. Study of a slide showed moderate poikilocytosis, no nucleated red cells and occasional large red cells which showed a slight amount of diffuse blueing. No punctate polychromatophilia was seen. Anisocytosis was rather marked. Most of the small cells were otherwise normal. The neutrophilic polymorphonuclear cells showed more than the usual polymorphism in the nucleus. Some had as many as seven distinct lobules. The

differential leukocyte count on the slide studied showed polymorphonuclear neutrophils, 45 per cent, lymphocytes, 36 per cent, mononuclear and transitional cells, 10 per cent, eosinophilic polymorphonuclears, 7 per cent, and basophilic polymorphonuclears, 2 per cent. Neurologic examination showed diminution of superficial sensation in the great toe, fingers and lateral aspect of the left ankle, where vibratory sensation was also affected. The tendon reflexes were normal, save for hyperactive patellar reflexes. No pathologic signs referable to the pyramidal tract were elicited. The Romberg sign was slightly positive. Doctor Catton was inclined to ascribe the origin of the patient's symptoms to the cord rather than to the peripheral nerves. Doctor Reed believed that the picture was one of sprue rather than of pernicious anemia, despite definite pernicious features in the blood. The diet outlined included a high protein content with liver. The patient, who lives in another city, has been infrequently seen by us but has carefully observed his condition himself and controlled his treatment. In April 1935 he wrote "At present there is slight remnant of paresthesia in the toes and fingers. The spot on the inner aspect of the left ankle is improved but still shows impaired sensation. Recovery of sensation in the toes and fingers is practically complete. The tendon reflexes are much less active and practically normal. Coordination of balance and finger movements is recovered almost completely, being 99 per cent plus. I have depended for the most part on fresh liver, lightly cooked, either fried or broiled, and I have been eating liver in that form for eight years. The daily average intake is from  $\frac{1}{3}$  to  $\frac{1}{2}$  pound (152 to 227 Gm). Part of the time I have taken liver extract<sup>17</sup> to supplement, or in addition to, the fresh liver. I have not used the hypodermic form of liver extract for myself. I have also drunk from a pint to a quart (470 to 950 cc) of acidophilus milk daily. I have taken buttermilk but no hydrochloric acid since I started the liver diet. I usually have liver for breakfast and also have meat for dinner. I use a few vegetables but no dessert or concentrated carbohydrates. I take cream, butter and meat fats freely. My diet is high in fats and proteins in relation to carbohydrates. My red cell count has averaged 6,000,000 or more over a period of several years, but the blood counts have been few and far between."

The characteristic neurologic symptoms, achlorhydria and blood picture would in our opinion fairly classify this case as one of pernicious anemia with neurologic complications, this diagnosis being confirmed by the course and favorable response to liver therapy.

*Group 2*—This group comprises 3 cases

**CASE 6 (Observed for Seven Years)**—A woman, aged 70, an artist, was first seen in June 1928, she complained of unsteady gait, dysesthesias and a sore tongue. Examination revealed an atrophic glossitis, an ataxic gait, a suspicious extensor response of the left great toe, a positive Romberg sign and near absence of vibratory sensation in the lower extremities. The state of the inferior tendon reflexes was not noted. The blood showed a macrocytic anemia, the red cells numbered 3,200,000, and the hemoglobin content was 70 per cent. Ingestion of  $\frac{1}{2}$  pound (227 Gm) of liver daily resulted in marked improvement, the soreness of the tongue disappeared, and the dysesthesias and unsteadiness became much less marked. In 1929 because of her improvement the patient discontinued taking liver, and her symptoms became aggravated. When the ingestion of liver was resumed, the symptoms subsided. In February, 1935, at the age of 77 years, the patient was remarkably active and felt quite well, except that she had slight dysesthesias and a feeling of unsteadiness and stiffness of her knees, which was not perceptible in her gait. The blood count showed 4,400,000 red cells and 88 per cent hemoglobin.

There was a slight Romberg sign, vibratory sensation was absent in the lower extremities, there was a questionable Babinski sign on the right, the patellar reflexes were sluggish, and the ankle reflexes were absent. During this entire period the patient had been able to continue her professional activities of painting in water colors.

**CASE 7 (Observed for Seven and a Half Years)**—A woman, aged 52, was first observed in the fall of 1927, complaining of dysesthesias in the extremities of one year's duration. She presented a typical picture of combined system disease of the cord and glossitis and a blood picture of macrocytic anemia, with 2,000,000 red cells and 46 per cent hemoglobin. She was given liver orally, in two months this treatment resulted in a rise of the number of red blood cells to 4,700,000, and of the hemoglobin content to 90 per cent, this was associated with remarkable betterment in her general physical and neurologic condition, the dysesthesia and ataxia becoming less marked. In April 1928 the pathologic signs referable to the pyramidal tract were lost. The blood counts, which attained a maximum of 4,900,000 in 1929, have been maintained at over 4,000,000 in subsequent years (on May 7, 1935, there were 4,750,000 red cells and 74 per cent hemoglobin), there has been a practically stationary condition in the patient's neurologic status, her weight has been maintained, she has experienced a feeling of well-being, there has been no return of glossitis, and gait and ability to walk and coordination have remained practically the same. This patient, therefore, has had a fairly satisfactory course for over seven years as a result of continuous liver therapy not precisely controlled, as the patient, who lives in a nearby town, comes to the office infrequently and must be urged to maintain her treatment because of her good performance and feeling of good health.

**CASE 8 (Observed for Three Years)**—A woman, aged 57, came to the clinic in September 1931, complaining of dysesthesias. Examination showed diminution of vibratory sensation, a positive Romberg sign, hyperactivity of the knee jerks, absence of ankle jerks, and a questionable Babinski sign. The red blood cells numbered 2,400,000 and the hemoglobin content was 59 per cent. The blood picture was that of macrocytic anemia. There was no free hydrochloric acid in the gastric contents. The patient was given liver extract<sup>17</sup> by mouth in large doses, and on Feb. 29, 1932, her red blood cells numbered 4,900,000 and the hemoglobin content was 97 per cent. She was then given 5 cc. of a solution of liver extract<sup>17</sup> intramuscularly each week, this therapy was continued until the patient was last seen, on Nov. 5, 1934, when her red cell count was 4,700,000 and the hemoglobin content was 93 per cent. Although dysesthesias were still present, her knee jerks were of normal intensity and her plantar reflex was in flexion. Otherwise the neurologic status was as before she received treatment.

#### COMMENT

The foregoing report of cases gives fair evidence of the specific action of liver on the neural manifestations of pernicious anemia in controlled, sustained adequate therapy. Cases are detailed in which the erythrocyte count was maintained at 5,000,000 for a year or more. Reference is particularly directed to case 1 (group 1), in which progression occurred during inadequate oral treatment consisting of what is ordinarily considered as maintenance dosage, yet in which marked improvement occurred after adequate parenteral therapy. The continued favorable response in this case (over three years) to parenteral

therapy suggests the effect of treatment to be one of replacement therapy rather than of temporary effectiveness. In case 3 (group 1) the clinical diagnosis of combined sclerosis after treatment could not be made from the clinical findings alone.

In contrast to the adverse reports of others, it is worthy of emphasis that in certain of these reports parenteral therapy was used in only a small number of cases and that the erythrocyte counts, as a rule, were below a figure reasonably to be designated as normal. The interpretation of neurologic signs on which Grinker and Kandel have laid so much emphasis in several of their cases may be influenced by several considerations: the variability of individual response from one examination to another, the probability of peripheral myelinic degeneration and, the most important consideration of all, whether abeyance of function in a neuron is always due to structural alteration or may be due to a reversible functional impairment. Our experience in cases of acute poliomyelitis is in favor of the latter contention. It is freely admitted that a structurally impaired central neuron is incapable of regeneration and that in such cases the degenerative process is merely arrested.

Another important consideration is the individual response to oral therapy and parenteral therapy. Whereas one patient may attain a satisfactory result from oral administration of liver, another may respond satisfactorily only to parenteral administration. Here again one may draw an analogy with syphilis.

Definite conclusions based on results of therapy at a time when liver therapy was at an early stage of development are scarcely applicable at present and may be compared with the earliest and unsatisfactory experience with digitalis therapy. It would be unfortunate, in our opinion, should the idea gain ground that the neural changes in pernicious anemia are due to something other than the deficiency causing the general picture of pernicious anemia and that, despite treatment, physicians may give their patients no assurance that their neurologic signs will not progress. Although the number of adequately treated patients is small, the results have an added significance in that there is no record in the series of progression in adequately treated patients.

#### CONCLUSIONS

Reports are submitted of the results of sustained, adequate and controlled treatment of patients with neurologic complications of pernicious anemia.

Adequate treatment as defined and illustrated is efficacious in both arresting and improving neurologic complications of pernicious anemia.



# EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

## V DIETS CONTAINING WHOLE DRIED MEAT

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In previous reports<sup>1</sup> it was shown that partial nephrectomy is followed by a progressive development of polyuria, albuminuria, nitrogen retention, renal hypertrophy, hypertension and cardiac hypertrophy. Feeding different concentrations of whole dried liver produced variations in this syndrome and in the pathologic changes in the kidney. The present report is concerned with the effect of whole meat on the partially nephrectomized rat. It demonstrates that whole dried meat causes changes in the syndrome similar to those produced by diets containing liver.

### EXPERIMENTAL METHODS

Details of the experimental procedures have been presented in previous papers<sup>1</sup>. In these as in former experiments the control animals included rats with both kidneys intact and unilaterally nephrectomized rats. The partially nephrectomized animals were those in which from 80 to 90 per cent of the total renal tissue was removed by a two stage operation.

Two procedures were used in the determination of renal function. The first was a determination of the volume, specific gravity and protein of the urine after the animal was without food and water for twenty-four hours. This will be called the concentration test. Second, a week later, a modified Addis urea clearance test was carried out as follows. Food was withdrawn for sixteen hours, the animal was then given a 5 per cent solution of urea by stomach tube, the number of cubic centimeters being equal to one fortieth of the number of square centimeters of surface area. The voided urine was collected for six hours, and residual urine was obtained by massaging the abdominal wall, blood was obtained by clip-

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The pathologic study was made by Dr. Paul Kimmelstiel of the Department of Pathology, the Medical College of Virginia.

This investigation was made possible by a grant from the National Live Stock and Meat Board and by the Edward N. Gibbs Prize Fund of the New York Academy of Medicine.

1 (a) Chanutin, Alfred, and Ferris, E. B., Jr. Experimental Renal Insufficiency Produced by Partial Nephrectomy. I. Control Diet, *Arch. Int. Med.* **49**: 767 (May) 1932. (b) Chanutin, Alfred. Experimental Renal Insufficiency Produced by Partial Nephrectomy. III. Diets Containing Whole Dried Liver, Liver Residue and Liver Extract, *ibid.* **54**: 720 (Nov.) 1934.

ping the tail at the middle of this six hour period. The funnel of the metabolism cage was not washed, since it was assumed that only a negligible amount of urine dried on the surface. The urine and blood were not analyzed in the presence of diarrhea. The amount of urea in the blood and urine was determined by the gasometric urease method of Van Slyke<sup>2</sup>. The urea ratio was calculated from the formula  $\frac{\text{urea excretion per hour}}{\text{urea in 100 cc of blood}}$ . The specific gravity of the urine was corrected for the amount of albumin by applying the equation of Lashmet and Newburgh,<sup>3</sup> specific gravity correction =  $0.003 \times \text{percentage of protein}$ . The correction was applied to the values for specific gravities with the realization that the factor was intended for urine from human subjects. No corrections were made for urinary volumes under 4 cc, since the excretion of protein was not estimated in these cases.

From about five to seven days after the determination of the urea ratio, the animal was killed. Blood pressure readings were obtained by inserting a needle into the carotid artery while the animal was under ether anesthesia. The heart and kidneys were weighed immediately after removal, having been dried of superficial blood and urine on filter paper. No attempt was made to differentiate the effect of sex on the weight of the kidneys. The surface area was calculated

TABLE 1—*Composition of Rations*

Diet	Concentration of Component in Diet, Percentage						
	Dried Whole Meat	Starch	Lard	Cod Liver Oil	Dried Yeast	Salt Mixture	Nitrogen
M 10	10	62	14	5	5	4	1.7
M 20	20	52	14	5	5	4	2.8
M 40	40	32	14	5	5	4	5.2
M 80	80		6	5	5	4	10.0

from the weight of the animal by the formula of Lee<sup>4</sup>. The ratio of the weight of the heart and kidneys to the surface area is expressed by  $\frac{H \cdot W}{S \cdot A}$  and  $\frac{K \cdot W}{S \cdot A}$ , respectively.

Four experimental diets were used and were designated as M 10, M 20, M 40 and M 80, in accordance with the percentage of whole dried meat which they contained. The composition of the diets is shown in table 1. The diets differed chiefly in the percental concentration of whole dried meat, which was the chief source of protein. A large quantity of cold storage lean meat was ground without loss of tissue juice, dried in a large steam-heated container and ground to a fine powder.

For histologic study, the kidneys were fixed in a dilute solution of formaldehyde U S P (1:10), embedded in paraffin and stained with hematoxylin and eosin. The pathologic findings were classified independently by Dr. Paul Kimmelstiel, of the department of pathology of the Medical College of Virginia, on the following basis:

The changes in the tubules are graded from 1 to 4 solely on the basis of dilatation. Grade 1 represents the slightest degree of recognizable dilatation, and grade 4 indicates the most marked. Changes in the epithelium of the tubules, such as

<sup>2</sup> Van Slyke, D. D. J. Biol. Chem. **73**: 695, 1927.

<sup>3</sup> Lashmet, F. H., and Newburgh, L. H. Specific Gravity of Urine as a Test of Kidney Function, J. A. M. A. **94**: 1883 (June 14) 1930.

<sup>4</sup> Lee, M. O. Am. J. Physiol. **89**: 24, 1929.

granules and vacuoles or enlargement and sloughing of cells, could not be expressed in numerical gradation, but in general these evidences of degeneration increased with the dilatation of the tubules

The earliest glomerular change is apparently manifested by swelling of the epithelial cells, which is followed by thickening and hyalinization of the connective tissue framework. In the most advanced stages, these pictures are complicated by adhesions of the glomeruli associated with proliferation of the parietal cells of Bowman's capsule and necrosis of the capillary loops. These changes are of focal distribution. In grading the glomerular damage, the numerals from 1 to 4 give a general impression of the relative severity of these focal degenerative and inflammatory changes.

#### EXPERIMENTAL RESULTS AND ANALYSIS OF OBSERVATIONS

*Controls*—A summary of results, including blood pressure,  $\frac{H}{S} \frac{W}{A}$  and  $\frac{K}{S} \frac{W}{A}$  ratios, response to the concentration test and urea ratio, for one hundred and fifty-one rats which were intact or unilaterally nephrectomized is presented in table 2. The  $\frac{K}{S} \frac{W}{A}$  ratios and the urea ratio are supplemented by additional values for a special group of control animals.

Of the seventy-three intact animals, there was but one with an elevated blood pressure (150 mm). There were four with blood pressures above 140 mm among the seventy-eight unilaterally nephrectomized animals. The mean values for blood pressure in the two groups on each diet were so close together that both groups were used in calculating the standard error for each diet. It can be seen that the various diets caused no significant changes in the blood pressure. The mean values for the  $\frac{H}{S} \frac{W}{A}$  ratio in the different dietary groups are remarkably constant, and the standard errors are very small. There is therefore a constant relationship between this ratio and the blood pressure in control animals.

There is a progressive increase in the  $\frac{K}{S} \frac{W}{A}$  ratio with the increased protein intake (chart 1). If the average  $\frac{K}{S} \frac{W}{A}$  ratio for the intact M 10 animals is considered as 1, the intact animals on the M 20, M 40 and M 80 diets show comparative ratios of 1.10, 1.19 and 1.33, respectively. If the ratio for the unilaterally nephrectomized animals on the M 10 diet is considered as 1, the increases were 1.06, 1.19 and 1.44, respectively. These results indicate that the most marked hypertrophy was obtained in the unilaterally nephrectomized rats on the M 80 diet.

If a comparison of the  $\frac{\text{average kidney weight of unilaterally nephrectomized rats}}{\text{average kidney weight of intact rats}}$  ratios is made, values of 0.69, 0.67, 0.69 and 0.75 are obtained for the animals on the M 10, M 20, M 40 and M 80 diets, respectively. If renal hypertrophy is due to the increased excretory load, it would be assumed that these ratios would become progressively greater as the amount of protein ingested increased, since the single kidney must do

TABLE 2—*Observations on Control Animals Fed a Variety of Diets*

Rats	Renal Condition and Diet	Value	Weight, Gm	Duration of Experiment, Days	Blood Pressure, Mm	Heart Weight		Kidney Weight		Twenty-Four Hour Urine Concentration Test		Urine Urea per Hour
						Surface Area	$\times 100$	Surface Area	$\times 100$ †	Volume, Cc	Specific Gravity	Urea in 100 Cc Blood
15	2 kidneys M 10	Minimum	178	14	106	0.139		0.312		1.0	1.0297	28
		Maximum	320	203	170	0.189		0.195 (30)		1.6	1.0517	70 (40)
		Average			123	0.175		0.101 $\pm$ 0.008		2.6	1.0193	50 $\pm$ 1.03
16	1 kidney M 10	Minimum	130	14	106	0.141		0.210		0.7	1.0201	23
		Maximum	354	248	138	0.212		0.378 (27)		3.9	1.0375	72 (43)
		Average			*121 $\pm$ 2.6	0.172		0.217 $\pm$ 0.008		2.1	1.0193	95 $\pm$ 1.11
21	2 kidneys M 20	Minimum	194	34	106	0.141		0.350		0.7	1.0355	35
		Maximum	432	207	131	0.207		0.550 (31)		1.5	1.0676	80 (42)
		Average			122	0.182		0.110 $\pm$ 0.008		2.7	1.0401	60 $\pm$ 2.10
22	1 kidney M 20	Minimum	178	53	106	0.137		0.252		0.5	1.0154	29
		Maximum	330	286	138	0.204		0.332 (33)		1.1	1.0511	59 (41)
		Average			*121 $\pm$ 1.20	0.172		0.293 $\pm$ 0.005		2.0	1.0193	12 $\pm$ 1.15
17	2 kidneys M 10	Minimum	188	29	108	0.155		0.170		1.7	1.0300	0
		Maximum	410	225	12	0.204		0.623 (28)		5.5	1.0679	42 (11)
		Average			120	0.177		0.177 $\pm$ 0.011		3.1	1.0513	62 $\pm$ 2.11
19	1 kidney M 10	Minimum	181	66	108	0.148		0.294		1.2	1.0276	28
		Maximum	411	219	146	0.232		0.378 (30)		4.7	1.0380	55 (30)
		Average			*122 $\pm$ 1.45	0.173		0.170 $\pm$ 0.007		1.1	1.0514	12 $\pm$ 1.50
20	2 kidneys M 80	Minimum	206	29	104	0.112		0.485		2.3	1.0357	17
		Maximum	341	203	138	0.206		0.648 (31)		1.0	1.0641	103 (33)
		Average			122	0.170		0.333 $\pm$ 0.010		2.6	1.0516	66 $\pm$ 2.90
21	1 kidney M 80	Minimum	176	45	96	0.143		0.323		0.4	1.0390	23
		Maximum	411	203	150	0.193		0.171 (33)		1.8	1.0809	66 (43)
		Average			*123 $\pm$ 1.87	0.167		0.397 $\pm$ 0.009		2.6	1.0555	11 $\pm$ 1.58

\* Average and standard error for control animals on a specific diet

† The  $\frac{K}{S} \frac{W}{A}$  ratio and the urea ratio are represented by a larger number of animals which are indicated by the figures in parentheses

twice its normal work. The results obtained were unusually uniform, with the possible exception of those obtained in the group receiving the M 80 diet.

The volume of urine excreted during the concentration test was 5 cc. in only two cases and was between 4 and 5 cc. in eight cases. The vast majority of the volumes were found to be between 1 and 3 cc.

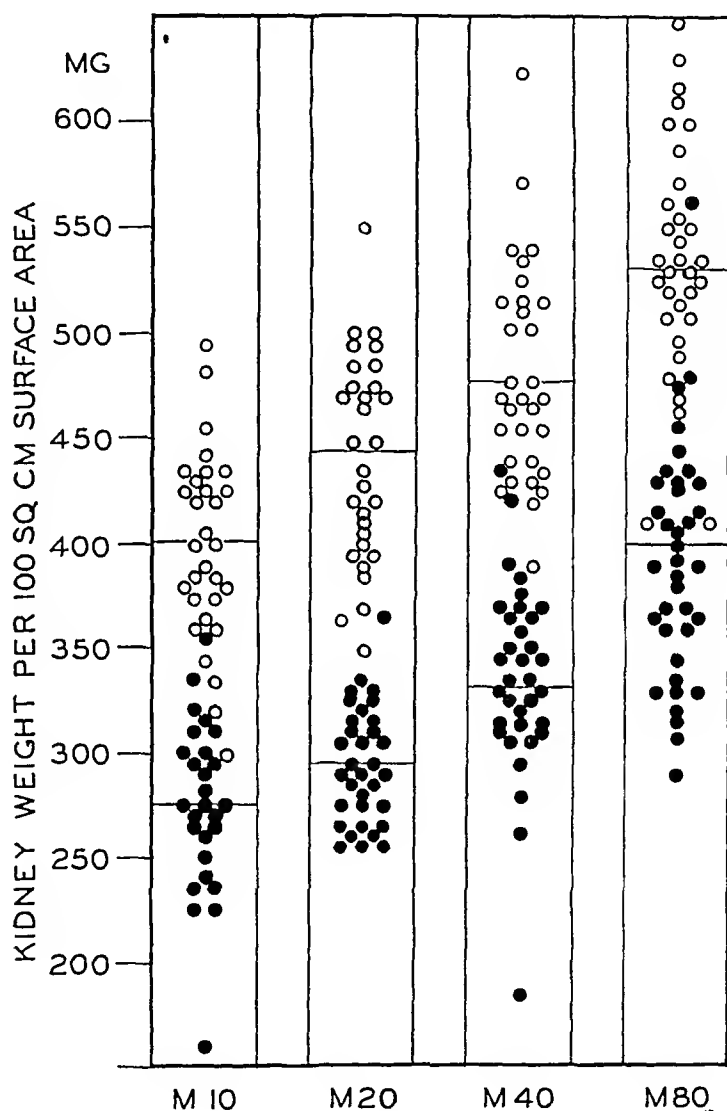


Chart 1—The effect of diet on the  $\frac{KW}{SA}$  ratio in intact and in unilaterally nephrectomized rats. The unshaded circles indicate the animals with two kidneys, the shaded circles indicate those with one kidney.

The average values for volume are uniform in the eight groups, and there seems to be no significant effect of diet on the volume of urine obtained during the concentration test. Although there was a great individual variation in the specific gravity, the averages for each group appear to be representative, the urine from animals on the diet con-

TABLE 3—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 10 Per Cent of Whole Meat*

Rat	Duration of Experiment, Days	Surface Area, Sq Cm	Blood Pressure, Min	Heart Weight	Kidney Weight	Twenty Four Hour Urine Concentration Test			Urea Ratio	Pathologic Change	
				Surface Area × 100	Surface Area × 100	Volume, Ce	Specific Gravity	Albumin, Gm		Tubule	Glomerulus
1	14	234	122	0 137	0 089	8 0	1 0199				
2	14	237	152	0 136	0 110	6 5	1 0222	0 008			
3	43	279	122	0 197	0 146	6 0	1 0226	0 004			
4	53	292	128	0 159	0 133	8 2	1 0255	0 005			
5	53	235	112	0 175	0 155	4 4	1 0204	0 003			
6	57	248	142	0 198	0 145	5 9	1 0260			1	0
7	60	283	130	0 165	0 169	4 3	1 0281				
8	60	222	126	0 149	0 101	3 6	1 0280				
9	61	222	110	0 169	0 117	3 7	1 0236				
10	61	224	104	0 137	0 131	3 4	1 0272				
11	61	271	130	0 164	0 132	3 3	1 0332				
12	101	282	122	0 198	0 179	3 5	1 0328		15		
13	101	257	168	0 231	0 127	8 8	1 0174	0 058			
14	101	326	138	0 209	0 163	4 5	1 0318	0 016	16		
15	101	274	118	0 200	0 146	4 7	1 0254				
16	128	286	130	0 186	0 177	3 6	1 0335	0 012	16		
17	135	339	140	0 202	0 214	8 6	1 0214			1	0
18	138	302	144	0 184	0 167	5 2	1 0248	0 040		1	0
19	138	295	126	0 192	0 181	4 2	1 0220	0 018		1	0
20	142	275	126	0 184	0 240	3 6	1 0379	0 028	22		
21	142	248	132	0 177	0 170	3 5	1 0343	0 001	17		
22	142	232	126	0 213	0 186	4 9	1 0271	0 001	16		
23	142	270	126	0 166	0 207	4 1	1 0310	0 002	21		
24	142	284	126	0 168	0 169	3 6	1 0376		18		
25	142	299	148	0 178	0 176	2 2	1 0468		21		
26	142	228	146	0 170	0 160	3 3	1 0249		11		
27	142	266	132	0 176	0 169	2 9	1 0379		19		
28	142	275	136	0 177	0 204	2 0	1 0406		22		
29	146	341	154	0 172	0 187	6 1	1 0247	0 062	14		
30	146	304	114	0 192	0 159	4 5	1 0240		12		
31	146	336	114	0 176	0 161	3 6	1 0286		11		
32	146	260	162	0 169	0 144	10 2	1 0167	0 072	9		
33	146	263	164	0 183	0 152	6 8	1 0167	0 024			
34	147	320	144	0 194	0 215	2 8	1 0289		16		
35	147	254	142	0 171	0 171	3 6	1 0317		9		
36	147	258	126	0 182	0 142	3 2	1 0319		10		
37	152	328	208	0 250	0 189	9 2	1 0171	0 021			
38	152	191	132	0 168	0 155	1 8	1 0257				
39	152	202	188	0 233	0 201	1 8	1 0326		9		
40	155	262	192	0 226	0 200	9 2	1 0140	0 038	12		
41	155	334	154	0 185	0 183	4 0	1 0312		24		
42	155	346	148	0 185	0 179	4 1	1 0297		15		
43	159	266	150	0 184	0 217	4 5	1 0267	0 009		0	0
44	159	273	152	0 183	0 226	2 9	1 0281			1	0
45	168	322	124	0 183	0 186	5 4	1 0288	0 005	16	1	0
46	168	320	152	0 208	0 235	4 6	1 0273	0 059	15	2	I
47	168	336	148	0 180	0 170	3 8	1 0291		13	1	0
48	168	318	130	0 160	0 167	2 6	1 0308		12		
49	168	283	134	0 169	0 153	5 3	1 0267	0 011	14	1	I
50	179	330	142	0 186	0 197	4 1	1 0290		16		
51	179	358	136	0 186	0 272	4 8	1 0312	0 080	39		
52	179	318	154	0 202	0 202	5 2	1 0173	0 018	20		
53	206	250	186	0 212	0 270					1	I
54	213	322	168	0 216	0 262						
55	213	315	150	0 216	0 175					2	I
56	226	345	138	0 200	0 204	3 3	1 0290		21		
57	226	216	178	0 248	0 287	6 7	1 0160	0 002	7		
58	226	278	154	0 212	0 220	3 8	1 0295		4		
59	232	326	142	0 284	0 252						
60	238	299	118	0 194	0 154	2 5	1 0465			1	I
61	238	320	150	0 244	0 219	3 0	1 0498			2	II
62	238	304	138	0 183	0 200	3 0	1 0483			1	I
63	246	282	134	0 162	0 149					1	0
64	251	272	150	0 176	0 167					0	0
65	251	268	128	0 161	0 134					0	0
66	263	346	126	0 230	0 189	6 3	1 0300	0 061		1	0
67	263	310	130	0 202	0 213	3 7	1 0372			1	0

aining the lowest amount of meat showed the lowest specific gravity (1.0433), and that from the animals on the diet containing the highest amount of meat showed the highest average value (1.0555). The value for urinary protein, determined in five animals, was found to be 0.010, 0.020, 0.024, 0.042 and 0.047 Gm., respectively.

The individual values for the urea ratio,  $\frac{\text{urea excreted in one hour's urine}}{\text{urea in 100 cc. of blood}} \times 100$ , varied appreciably in the control animals on various diets. The average values for the ratio in animals with both kidneys intact were

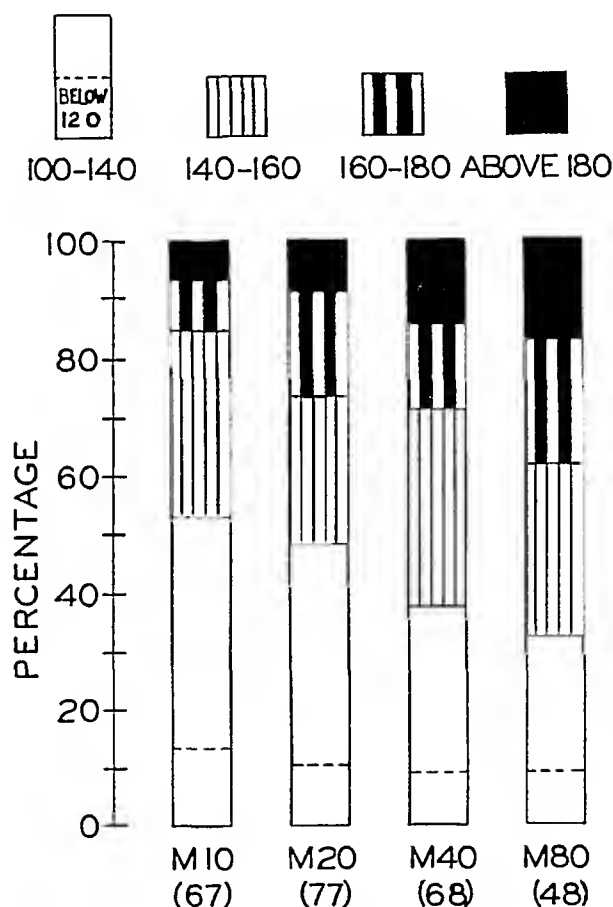


Chart 2—The effect of diet on the blood pressure of partially nephrectomized rats

50, 60, 62 and 66 for the groups receiving the M 10, M 20, M 40 and M 80 diets, respectively, whereas the ratios for the unilaterally nephrectomized animals on the same diets were 35, 42, 42 and 41. This shows that the ability to excrete urea increases markedly in the intact animals fed the diets containing a higher percentage of protein but is relatively constant in the animals with one kidney. A comparison of the  $\frac{\text{average urea ratio of unilaterally nephrectomized rats}}{\text{average urea ratio of intact rats}}$  ratios gives values of 0.70, 0.70, 0.68 and 0.62. This indicates decreased renal function in the unilaterally nephrectomized animals as the protein content of the diet

TABLE 4—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 20 Per Cent of Whole Meat*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight	Kidney Weight	Twenty Four Hour Urine Concentration Test			Urea Ratio	Pathologic Change	
				Surface Area × 100	Surface Area × 100	Volume, Cc.	Specific Gravity	Albumin, Gm.		Tubule	Glomerulus
1	14	221	126	0 164	0 119	7 8	1 0199	0 003			
2	14	248	144	0 148	0 125	7 4	1 0254	0 009			
3	14	231	162	0 159	0 134						
4	14	283	114	0 170	0 148	5 2	1 0310	0 009			
5	55	255	162	0 232	0 180	9 8	1 0235	0 240		1	0
6	55	248	130	0 148	0 118	7 6	1 0190	0 025		1	0
7	55	293	164	0 173	0 174	5 9	1 0260	0 014			
8	57	304	122	0 179	0 212	2 6	1 0370			1	0
9	57	252	104	0 154	0 161	3 0	1 0308			0	0
10	57	307	126	0 193	0 142	6 2	1 0207	0 031			
11	57	306	126	0 175	0 150	10 6	1 0212	0 037		0	I
12	57	294	128	0 184	0 206	8 6	1 0222	0 100		1	I
13	57	314	172	0 249	0 191	8 0	1 0206	0 069		2	I
14	57	364	142	0 205	0 193	4 9	1 0367	0 043			
15	57	294	132	0 179	0 188	4 0	1 0333	0 005		0	0
16	57	283	172	0 210	0 163	6 3	1 0278	0 045		2	I
17	61	322	136	0 187	0 178	8 8	1 0273	0 051			
18	61	301	118	0 174	0 140	7 6	1 0286	0 027			
19	62	339	132	0 195	0 203	6 3	1 0200	0 029			
20	62	339	94	0 204	0 208	7 5	1 0247	0 014			
21	87	329	190	0 244	0 213	8 6	1 0222	0 088	7		
22	90	368	118	0 178	0 217	6 2	1 0320		15		
23	90	341	154	0 197	0 249	11 3	1 0198		9	1	I
24	90	307	120	0 171	0 200	6 7	1 0244		23		
25	90	286	130	0 164	0 206	5 8	1 0262		13		
26	105	389	152	0 214	0 214	6 6	1 0270	0 069	9		
27	107	362				7 0	1 0284	0 068	8		
28	114	228	222	0 210	0 193	11 6	1 0155	0 045	7		
29	120	324	138	0 166	0 216	6 8	1 0241	0 056			
30	120	324	204	0 214	0 306	11 0	1 0229	0 168	11		
31	122	386	118			4 0	1 0397				
32	130	372	122	0 178	0 208	7 2	1 0229	0 027	12		
33	130	390	132	0 173	0 290	10 0	1 0229	0 124	12		
34	130	386	118	0 157	0 230	3 9	1 0321		26		
35	130	356	126		0 248	10 3	1 0173	0 061	13		
36	134	328	162	0 184	0 228	7 1	1 0230	0 053	16		
37	134	336	130	0 182	0 205	7 1	1 0242	0 063	17		
38	138	333	132	0 208	0 216	12 5	1 0168			1	I
39	138	364	132	0 209	0 205	6 0	1 0271	0 042		1	I
40	140	280	126	0 164	0 227	3 1	1 0407		23		
41	140	392	138	0 194	0 276	5 6	1 0345	0 129	29		
42	141	280	150	0 194	0 207	5 3	1 0198	0 041		1	I
43	141	270	116	0 188	0 192	3 4	1 0297				
44	141	270	176	0 188	0 294	11 3	1 0207	0 196		2	III
45	141	370	150	0 229	0 254	6 0	1 0157	0 045			
46	146	370	148	0 161	0 242	10 4	1 0204	0 050	6		
47	146	278	174	0 175	0 216	9 0	1 0181	0 061	5		
48	153	358	158	0 212	0 299	10 6	1 0180	0 078			
49	153	262	220	0 241	0 250	7 3	1 0165	0 001	4		
50	154	306	156	0 248	0 344	10 7	1 0215	0 176	7		
51	166	313	134	0 188	0 310	9 0	1 0209	0 097	16		
52	166	345	122	0 176	0 222	11 9	1 0178	0 069	11		
53	166	370	164	0 214	0 270	11 6	1 0191	0 050	8		
54	166	427	148	0 207	0 266	21 5	1 0178	0 300	14		
55	166	323	142	0 168	0 222	4 0	1 0365		27		
56	166	374	112	0 184	0 224	5 5	1 0311	0 037	20		
57	166	326	144	0 198	0 231	4 2	1 0391		24		
58	166	307	124	0 179	0 209	5 1	1 0331	0 027	20		
59	166	272	164	0 237	0 284	8 0	1 0181	0 068	5		
60	166	245	170	0 239	0 176						
61	171	306	204	0 257	0 210	9 5	1 0145			3	IV
62	171	395	128	0 179	0 240	2 8	1 0365			3	IV
63	178	328	158	0 183	0 252	5 6	1 0293	0 062	23	1	0
64	178	433	168	0 214	0 394	11 2	1 0241	0 137			
65	183	383	138	0 214	0 309	10 5	1 0251	0 190	12		
66	183	368	148	0 218	0 338	9 5	1 0253	0 175			
67	183	354	132	0 196	0 266	7 8	1 0270	0 137	14		
68	187	354	116	0 171	0 223	4 3	1 0333				
69	202	304	150	0 191	0 277	3 2	1 0322		14		
70	202	320	126	0 197	0 215	3 5	1 0469		16		
71	202	308	184	0 209	0 209	3 8	1 0296		13		
72	202	289	148	0 198	0 346	9 0	1 0282	0 132	7		
73	202	400	144	0 212	0 490	10 3	1 0202	0 090	10		
74	217	354	172	0 196	0 229	12 7	1 0156	0 088	1		
75	217	354	156	0 188	0 273	15 0	1 0172	0 114	3		
76	226	318	140	0 197	0 254	4 0	1 0350				
77	286	367	146	0 173	0 432	2 8	1 0245			1	0



increases These values are similar to those obtained in intact dogs<sup>5</sup> and rabbits<sup>6</sup> maintained on standard diets

Because the values listed in table 2 were fairly constant in all control animals, the following values have been taken as the limits of normal for all the animals blood pressure below 140 mm of mercury, urinary volume below 5 cc, urinary specific gravity above 1.04, urinary protein content below 0.05 and urea ratio above 30

*Effect of Diet on Experimental Animals in Good Health*—The effects of the M 10, M 20, M 40 and M 80 diets on partially nephrectomized rats are shown in detail in tables 3 to 6, respectively Charts 2 to 7 were prepared from these tables to facilitate comparisons of the effects of the different diets on the blood pressure, urinary volume, urinary specific gravity after correction was made for albumin, urinary protein, urea ratio and kidney weight, respectively

**Blood Pressure** The effects of diet on blood pressure are summarized in chart 2 There is a progressive decrease in the number of animals having blood pressures below 140 mm as the concentration of meat in the diet increases Conversely, the incidence of significant hypertension (over 160 mm) is definitely increased with diets containing more meat However, individual maximum values for blood pressure do not appear to be influenced by the diet Because of the relatively small number of rats killed during the first few months after operation, it is impossible to draw conclusions concerning the time of appearance and the ultimate incidence of increased blood pressures

The relationship between hypertension and the  $\frac{H}{S} \frac{W}{A}$  ratios varied with the different diets In the younger animals the relationship was poor as a general rule The correlation coefficients and their probable errors were calculated for the blood pressure and the  $\frac{H}{S} \frac{W}{A}$  ratio for each diet as follows M 10,  $0.43 \pm 0.065$  (substantial relationship), M 20,  $0.61 \pm 0.048$  (very substantial relationship), M 40,  $0.30 \pm 0.075$  (low relationship), M 80,  $0.47 \pm 0.076$  (substantial relationship) The low correlation coefficient found in the animals which were fed the M 40 diet cannot be explained These results, representing the partially nephrectomized animals only, do not show as high a degree of correlation as that obtained in previous reports<sup>7</sup> in which control animals were included

5 Rhoads, C. P., Alving, A. S., Hiller, A., and Van Slyke, D. D. *Am. J. Physiol.* **109**: 329, 1934

6 Addis, T., Myers, B. A., and Oliver, J. The Regulation of Renal Activity, *Arch. Int. Med.* **34**: 234 (Aug.) 1924

7 Chanutin, Alfred, and Barksdale, E. E. Experimental Renal Insufficiency Produced by Partial Nephrectomy II Relationship of Left Ventricular Hypertrophy, the Width of the Cardiac Muscle Fiber and Hypertension in the Rat, *Arch. Int. Med.* **52**: 730 (Nov.) 1933 Chanutin and Ferris<sup>1a</sup>

TABLE 5—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 40 Per Cent of Whole Meat*

Rat	Duration of Experiment, Days	Sur face Area, Sq Cm	Blood Pres sure, Mm	Heart Weight	Kidney Weight	Twenty Four Hour Urine Concentration Test				Pathologic Change		
				Surface Area × 100	Surface Area × 100	Volume, Cc	Specific Gravity	Albumin, Gm	Urea Ratio	Tu bule	Glo meru lus	
1	29	358	103	0 194	0 223							
2	29	316	138	0 183	0 188							
3	47	299	136	0 159	0 155	13 5	1 0150					
4	47	343	158	0 171	0 214	7 3	1 0270				3	I
5	47	249	180	0 169	0 183	6 1	1 0189				3	I
6	47	330	156	0 177	0 192	14 2	1 0174				2	I
7	47	323	124	0 195	0 206	13 6	1 0194				0	0
8	47	337	136	0 192	0 166	13 5	1 0185					
9	47	327	123	0 193	0 171	15 0	1 0177				1	I
10	50	274	138	0 199	0 236							
11	66	339	162	0 175	0 263	7 2	1 0276		15			
12	66	343	124	0 168	0 302	5 6	1 0443	0 009	24			
13	66	234	134	0 224	0 343	2 8	1 0634		20			
14	66	265	136	0 149	0 204	4 1	1 0229	0 000	6			
15	66	260	152	0 158	0 200	9 0	1 0174		4			
16	66	339	152	0 185	0 239	12 0	1 0169	0 038	3			
17	66	252	144	0 161	0 266	3 1	1 0246		13			
18	66	318	126	0 168	0 253	4 9	1 0410	0 010	15			
19	67	328	116	0 170	0 239	9 6	1 0273	0 040	13			
20	67	276	146	0 174	0 248	5 7	1 0274	0 002	17			
21	67	348	146	0 181	0 262	8 7	1 0312	0 017	13			
22	67	270	116	0 158	0 218	7 2	1 0228	0 034	11			
23	74	408	128	0 185	0 245	6 7	1 0302	0 096	16			
24	74	355	198	0 190	0 407	9 1	1 0278	0 177	8			
25	74	379	146	0 177	0 314	6 7	1 0285		16			
26	80	354	140	0 188	0 244	7 6	1 0271	0 080				
27	80	370	148	0 192	0 197	12 0	1 0176	0 002				
28	84	366	164	0 196	0 188	18 3	1 0162	0 122	3			
29	84	336	182	0 204	0 241	17 6	1 0147	0 027	8			
30	84	403	154	0 193	0 288	11 0	1 0215	0 093	4			
31	86	249	170	0 212	0 187							
32	87	238	163	0 246	0 216							
33	96	295	134	0 177	0 286	11 0	1 0162					
34	118	373	138	0 196	0 302	13 3	1 0213	0 107				
35	118	386	154	0 214	0 324	20 8	1 0156	0 196				
36	118	390	148	0 207	0 403	11 8	1 0241				3	II
37	118	340	208	0 300	0 258	20 5	1 0123	0 226	4		4	III
38	129	328	174	0 191	0 374	11 1	1 0190	0 117			3	IV
39	129	394	170	0 206	0 292	18 7	1 0158	0 168				
40	134	416	128	0 201	0 328				14		2	I
41	134	297	148	0 184	0 233				12			
42	134	372	144	0 188	0 298				8		4	II
43	134	314	126	0 169	0 339	11 4	1 0181	0 199	8		3	III
44	134	308	196	0 195	0 292	16 4	1 0150	0 164	7			
45	134	302	150	0 230	0 305	15 3	1 0162	0 075	8			
46	134	336	164	0 180	0 346	19 2	1 0148	0 144				
47	134	336	152	0 184	0 274	16 2	1 0145	0 121				
48	134	362	168	0 168	0 324	16 2	1 0177	0 183			2	III
49	134	343	128	0 160	0 346	8 7	1 0240	0 165				
50	134	336	158	0 190	0 405	17 1	1 0137	0 104				
51	134	355	144	0 166	0 467	9 5	1 0237	0 145				
52	134	306	148	0 156	0 300	7 1	1 0253	0 122				
53	141	308	166	0 195	0 302	13 0	1 0164	0 162	9			
54	142	390	184	0 248	0 324	17 2	1 0147	0 098	6		4	III
55	155	413	172	0 211	0 398	14 3	1 0202	0 236				
56	160	412	130	0 167	0 356	2 9	1 0565					
57	160	352	204	0 220	0 344	16 1	1 0171	0 262				
58	160	323	122	0 192	0 280	7 5	1 0272	0 140				
59	160	317	196	0 198	0 497	7 5	1 0247	0 157				
60	160	343	152	0 186	0 355	9 5	1 0207	0 144				
61	160	316	132	0 162	0 304	7 6	1 0180	0 110	9			
62	160	390	124	0 178	0 329	11 5	1 0193	0 086	11		3	II
63	160	308	154	0 192	0 286	9 1	1 0150	0 061	8		3	II
64	171	408	210	0 238	0 339							
65	179	458	150	0 230	0 437	11 8	1 0230	0 150				
66	179	318	180	0 264	0 407	10 6	1 0254	0 087				
67	225	314	146	0 240	0 364	18 3	1 0205	0 240	6			
68	225	370	138	0 185	0 339	1 0	1 0395					

Urine Concentration Test Chart 3 shows the effect of various diets on the urinary volume of partially nephrectomized animals. There is a progressive increase in the incidence and degree of polyuria with

TABLE 6—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 80 Per Cent of Whole Meat*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight	Kidney Weight	Twenty Four Hour Urine Concentration Test				Pathologic Change	
				Surface Area × 100	Surface Area × 100	Volume, Cc.	Specific Gravity	Albumin, Gm.	Urea Ratio	Tubule	Glomerulus
1	29	249	134	0.160	0.280						
2	29	254	112	0.179	0.264						
3	29	290	140	0.196	0.278						
4	29	283	142	0.212	0.338						
5	45	294	116	0.165	0.292	10.0	1.0210				
6	45	248	120	0.151	0.292	11.7	1.0181	0.134			
7	45	271	152	0.230	0.276	15.6	1.0176	0.234			
8	45	262	148	0.191	0.264	9.0	1.0206	0.082			
9	45					9.8	1.0206				
10	45	186	218	0.210	0.236					4	III
11	46	316	146	0.204	0.354	17.5	1.0200	0.247			
12	64	260	142	0.139	0.329	4.4	1.0285		14		
13	64	276	134	0.158	0.307	4.2	1.0287		16		
14	64	299	134	0.169	0.352	6.1	1.0245	0.030	10		
15	64	302	128	0.182	0.334	8.3	1.0223	0.028	13		
16	64	306	152	0.189	0.354	10.0	1.0260	0.017	8		
17	64	295	132	0.162	0.326	5.6	1.0275	0.017	16		
18	70	278	144	0.198	0.404	15.6	1.0134	0.134			
19	70	283	162	0.158	0.447	7.5	1.0207	0.058	13		
20	70	284	134	0.191	0.310	16.8	1.0156	0.150	12		
21	70	339	128	0.165	0.374	5.7	1.0296	0.030	19		
22	87	255	174	0.197	0.315	10.0	1.0193	0.108	5		
23	87	262	168	0.200	0.292	8.3	1.0195	0.092	7		
24	115	278	146	0.178	0.369	4.3	1.0319		19	2	I
25	115	272	148	0.173	0.467	7.2	1.0233	0.058	14	4	III
26	115	275	166	0.211	0.420	14.1	1.0160	0.152	6	4	IV
27	115	341	165	0.245	0.532	24.0	1.0160	0.322	9	4	III
28	115	272	148	0.206	0.485	13.4	1.0175	0.162	11	2	III
29	120	268	158	0.171	0.400	11.7	1.0169	0.113	5		
30	121	278	158	0.161	0.484	12.1	1.0151	0.039	2	4	III
31	121	242	122	0.142	0.326	8.5	1.0189	0.030	7		
32	134	282	190	0.176	0.432	9.2	1.0161	0.081		4	IV
33	143	383	130	0.192	0.404	10.7	1.0247	0.154		2	I
34	143	379	160	0.201	0.380	17.9	1.0187	0.254		2	I
35	143	307	140	0.188	0.365	11.5	1.0200	0.190		2	I
36	143	380	118	0.196	0.362	10.7	1.0280	0.114		2	I
37	148	275	190	0.286	0.570	9.5	1.0249	0.330		4	IV
38	153	312	164	0.206	0.403	10.8	1.0215	0.197		3	III
39	153	299	154	0.228	0.380	13.3	1.0200	0.222		3	II
40	153	374	142	0.212	0.580	13.2	1.0187	0.117			
41	154	289	168	0.158	0.527	18.1	1.0139	0.159	6	4	III
42	161	268	132	0.174	0.392	5.7	1.0261	0.064	17	2	II
43	161	275	138	0.162	0.358	4.5	1.0350	0.060	18	2	II
44	161	252	118	0.159	0.362	9.4	1.0177	0.111		2	III
45	161	304	120	0.153	0.274	4.9	1.0271	0.013	17	1	I
46	163	286	146	0.258	0.487	27.4	1.0165	0.276	4		
47	225	232	204	0.237	0.216					4	IV
48	225	330	174	0.228	0.543	24.3	1.0167	0.198			
49	225	240	198	0.229	0.467	12.2	1.0156	0.134			

graded increments of meat. A marked difference in the effect of diet is manifested in the animals which were fed the M 10 and M 20 diets, in which the urinary volumes within the normal range were 71 and 23 per cent of the total, respectively. Although the percentage distribution of urine volumes appears to be the same for the animals receiving

the M 40 and the M 80 diet, the average of the volumes for the group producing 15 cc or more is greater in the animals receiving the M 80 diet

Chart 4 shows the effect of diet on the specific gravity of the urine after allowance was made for the effect of proteinuria in the majority of cases. There were, however, a number of uncorrected specific gravities, and this chart represents, therefore, an approximation of the true results. It is seen that the ability to concentrate urine decreases in the animals fed the diets containing higher percentages of meat. In one case the specific gravity fell below 1.01.

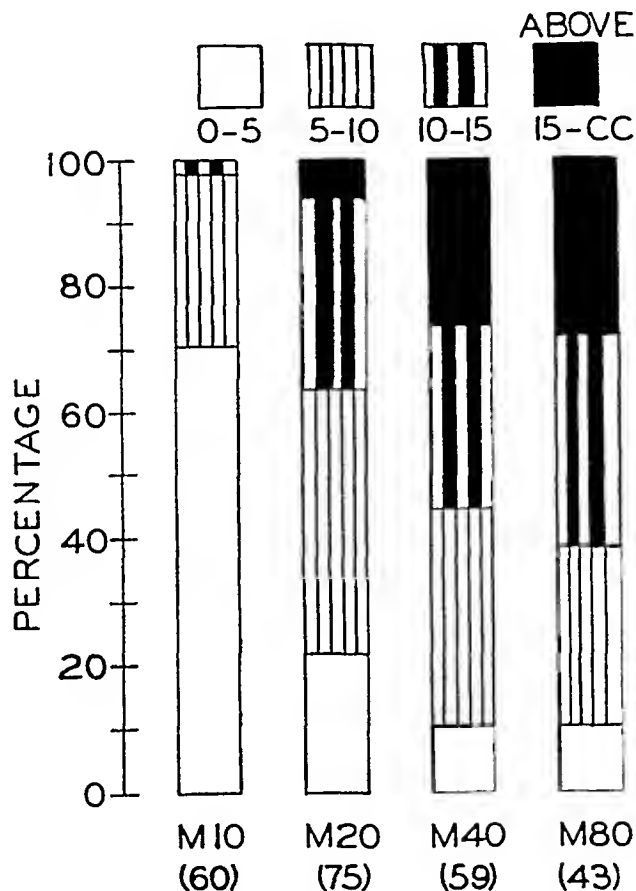


Chart 3—The effect of diet on the urinary volume of partially nephrectomized rats

Chart 5 summarizes the effects of diets on the excretion of protein. Of animals on the lowest meat intake, 80 per cent excreted amounts within normal limits, and the remainder did not excrete more than 0.1 Gm. The degree of proteinuria increased as the intake of meat was raised. Two animals on the M 80 diet excreted the largest amounts of protein (0.322 and 0.330 Gm) in the entire series.

**Urea Ratio.** Chart 6 summarizes the urea ratio values obtained in animals shortly before they were killed (values given in tables) and values obtained at various intervals before that time. There is a decrease in the ratios, which is most marked in the animals on the M 40 and M 80 diets.

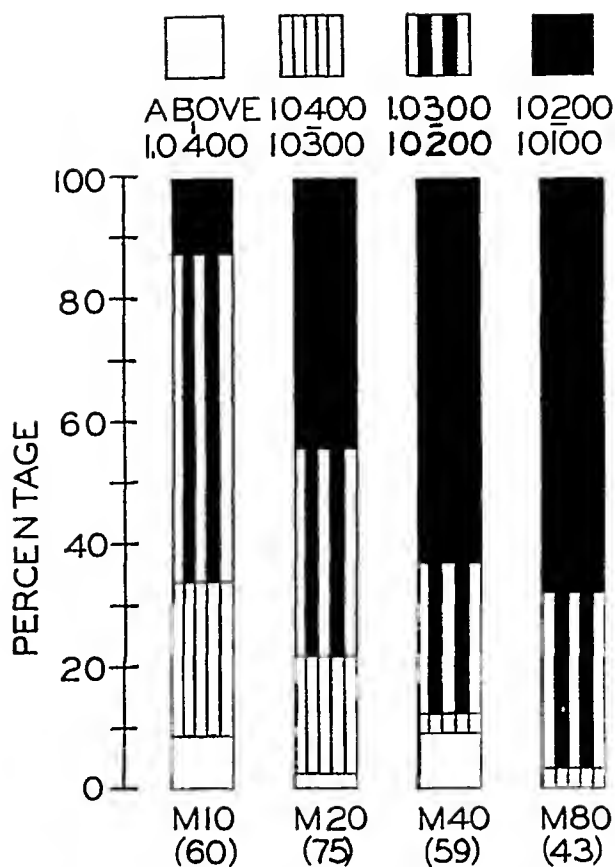


Chart 4—The effect of diet on the specific gravity (after correction for albumin) of the urine of partially nephrectomized rats

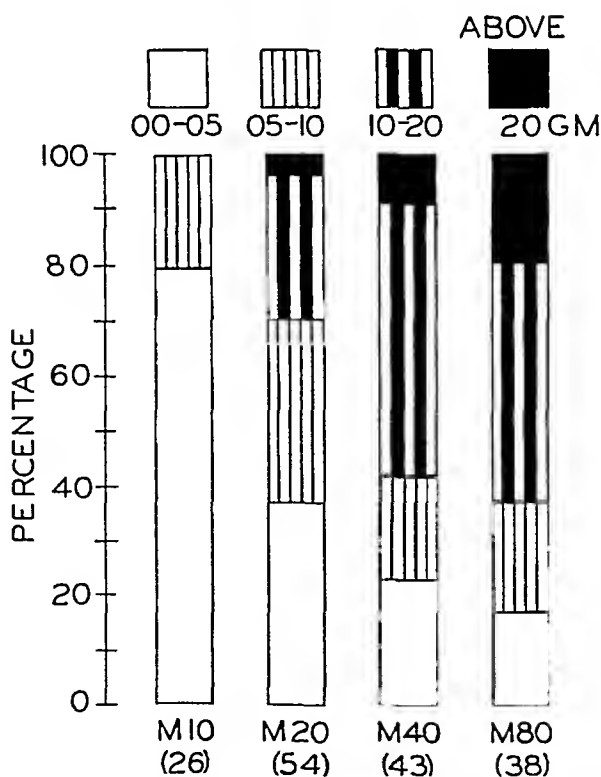


Chart 5—The effect of diet on the excretion of protein in the partially nephrectomized rat

The Relationship of Time After Operation to Urea Ratio The changes in renal function were dependent on the amount of meat in the diet. Animals on the M 10 diet generally maintained a fairly uniform urea ratio over a long period of time. The group on the M 20 diet showed variations in the results, many of the ratios remaining comparatively high for a long period while others showed relatively rapid decreases in renal function. With few exceptions, the animals on both the M 40 and the M 80 diet showed rather rapid drops in the

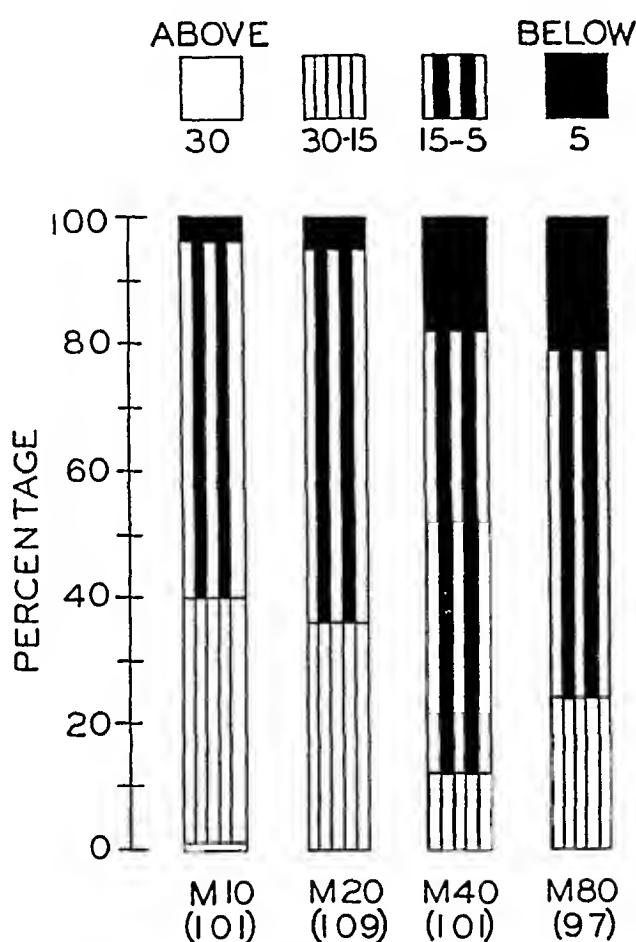


Chart 6—The effect of diet on the Addis ratio ( $\frac{\text{urea in one hour's urine}}{\text{urea in 100 cc of blood}} \times 100$ ) in partially nephrectomized rats

urea ratios. It was difficult to compare the changes in renal function at given time intervals in these animals because of the large individual variations.

When the urea ratio was determined during the first week after operation, the effect of diet was manifested during this short period. The animals on the M 40 and M 80 diets usually died shortly after the urea ratio was determined. The animals which were fed the M 20 diet were intermediate, in that some animals died and others survived, whereas none of those fed the M 10 diet died. Extremely low ratios

accompanied by high concentrations of urea were obtained in those animals which died during the "acute" period. Death was probably due to urea poisoning.

**Kidneys** The variations in the  $\frac{K}{S} \frac{W}{A}$  ratios are summarized in chart 7. The averages with the standard errors were as follows:  $0.179 \pm 0.005$ ,  $0.245 \pm 0.01$ ,  $0.289 \pm 0.01$  and  $0.359 \pm 0.014$  for the groups fed the

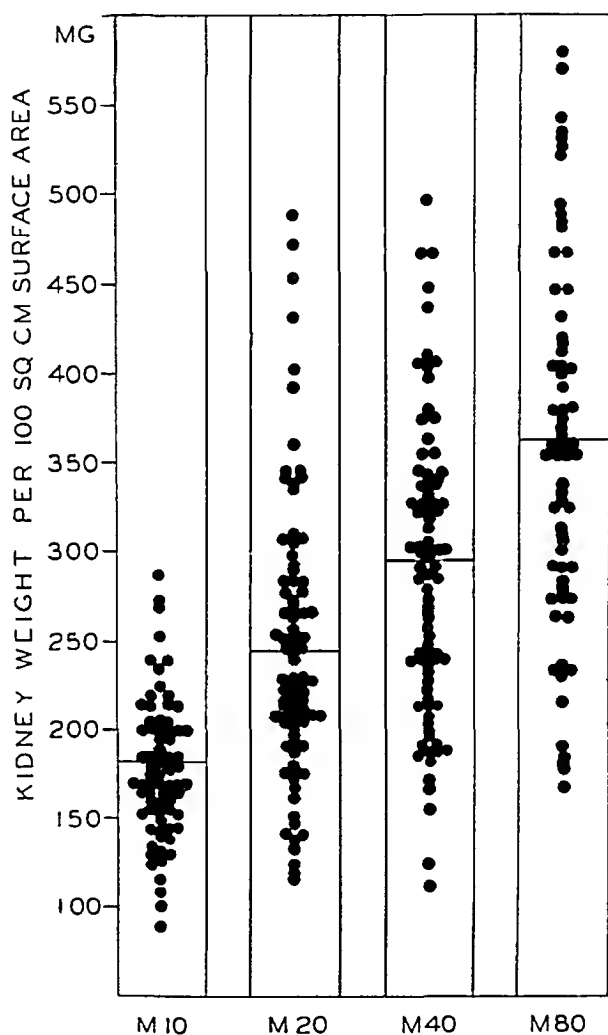


Chart 7—The effect of diet on the  $\frac{K}{S} \frac{W}{A}$  ratio in partially nephrectomized rats

M 10, M 20, M 40 and M 80 diets, respectively. The standard error was smallest for the group on the M 10 diet and greatest for the group on the M 80 diet, which suggests a greater reliability of the averages for the animals on the diet containing the lowest amount of meat. The greater variation in the  $\frac{K}{S} \frac{W}{A}$  ratios in the remaining groups may be due to variation in the amount of water or of renal substance or to a combination of both.

**Pathologic Changes** In most of the animals with severe glomerular changes there was evidence of hypertension. The degree of proteinuria appeared to be independent of glomerular or tubular changes. There was no good correlation between the specific gravity of the urine and the degree of pathologic change. An interesting but somewhat irrelevant observation was that the adrenal glands of the animals on the M 80 diet and of the acutely ill animals on the M 40 and M 80 diets manifested marked hemorrhages in the medulla and cortex, degeneration of part of the cortex and calcareous masses in the cortex.

*The Effect of Diet on Partially Nephrectomized Animals Becoming Acutely Ill*—Data for these animals are listed in table 7. The illness was either acute or chronic. Muscular tremors were usually present, occasionally convulsions were seen, the hair was ruffled, and the animal was sluggish. These animals manifested no characteristic combination of symptoms. The majority showed a marked loss of weight.

The blood pressure varied from 50 to 232 mm of mercury. In all animals with low blood pressure there was evidence of previous hypertension as manifested by dilated arteries and hypertrophied hearts. In calculating the  $\frac{H}{S} \frac{W}{A}$  ratios of these animals, no correction was made for the loss of weight. It should be noted that many of the  $\frac{K}{S} \frac{W}{A}$  ratios were particularly low, especially in the M 80 group. In practically every instance in which the concentration test was made, there was a consistently low value for renal function. Only two urea ratios were available, but other data suggest that low ratios are typical of the last stages of this syndrome. The pathologic findings indicated severe renal damage in all the dietary groups. In practically all rats fed the M 80 diet there were gross manifestations of hemorrhage in the adrenal glands, varying from a multiple punctate appearance to an almost solid red appearance.

#### COMMENT

When the relative effects of various percentages of liver<sup>1b</sup> and of meat in the diets of partially nephrectomized animals are compared, the experimental procedure and the nitrogen content of the respective diets being essentially the same, it will be seen that the variations in the urinary volume and specific gravity are not different, the excretion of protein was slightly greater for rats on several of the meat diets, and hypertension was more pronounced and frequent only in the rats fed the diets containing the highest percentage of meat. Since these differences observed in animals on the meat and liver diets were not uniform or striking, it was concluded that these diets have essentially the same effect on the renal function of partially nephrectomized rats.



TABLE 7—*Partially Nephrectomized Animals Killed While Acutely Ill*

Rat	Duration of Experi- ment, Days	Sur- face Area, Sq Cm	Blood Pres- sure, Mm	Heart Weight	Kidney Weight	Twenty Four Hour Urine Concentration Test				Pathologic Change	
				Surface Area × 100	Surface Area × 100	Volume, Cc	Specific Gravity	Albumin, Gm	Urea Ratio	Tu- bule	Glo- meru- lus
M 10											
1	115	220	93	0 202	0 136						
2	134	223	180	0 270	0 240						
3	140	231	170	0 229	0 185						
4	143	244	120	0 210	0 205						
5	192	246	114	0 275	0 194					4	IV
6	219	270	148	0 272	0 168						
M 20											
1	34	242	202	0 246	0 142						
2	71	255	66	0 232	0 247	5 0	1 0267	0 003	9		
3	87	257	98	0 230	0 253					2	III
4	101	254	66	0 214	0 278					3	II
5	101	291	196	0 279	0 402					3	III
6	106	358	174	0 254	0 177						
7	107	345	228	0 253	0 267						
8	109	363	138	0 253	0 311					3	III
9	123	339	206	0 256	0 453					3	III
10	124	292	110	0 289	0 472					3	
11	126	355	124	0 254	0 346						
12	129	242	108	0 247	0 264						
13	157	354	232							4	IV
14	167	373	216	0 246	0 340					3	IV
15	168	334	222	0 247	0 266					4	III
16	202	390	164	0 249	0 229	13 9	1 0162	0 106	5		
17	238	332	76	0 238	0 256						
18	239	335	176	0 294	0 284						
19	291	392	156	0 321	0 338						
M 40											
1	13	212	106	0 134	0 112						
2	32	171	96	0 181	0 214						
3	57	244	118	0 227	0 410						
4	79	346	206	0 230	0 244						
5	79	260	174	0 256	0 125						
6	79	349	196	0 247	0 328						
7	81	355	194	0 146	0 448						
8	87	243	164	0 216	0 189						
9	92	306	194	0 257	0 374						
10	94	293	150	0 258	0 240						
11	118	324	120	0 246	0 191						
12	125	334	180	0 254	0 320						
13	128	363	166	0 231	0 380						
14	136	314	64	0 278	0 228						
15	139	349	160	0 266	0 307						
16	150	339	80	0 264	0 329						
17	179	289	66	0 224	0 467	19 0	1 0195	0 260			
M 80											
1	37	238	104	0 163	0 233					1	I
2	52	272		0 218	0 274						
3	53	282	44	0 239	0 378					4	IV
4	56	217	50	0 219	0 191					4	IV
5	56	289	166	0 258	0 232	17 0	1 0173	0 172		3	II
6	57	282	48	0 206	0 185	18 0	1 0173	0 266		4	III
7	57	246	196	0 219	0 178	12 3	1 0180			4	IV
8	57	270	186	0 254	0 181	14 7	1 0149	0 052		4	II
9	58	216	150								
10	63	281	152	0 213	0 360						
11	77	245	118	0 248	0 361						
12	77	291	216	0 215	0 535					3	II
13	81	257	178	0 218	0 273						
14	85	286	76	0 261	0 413						
15	93	314	136	0 236	0 526					4	III
16	94	227	170	0 165	0 167						
17	112	270	194	0 242	0 418					4	IV
18	119	214	34	0 268	0 234						
19	126	267	98	0 252	0 301					3	III
20	135	274	80	0 233	0 360					4	IV
21	135	218	94	0 210	0 494						
22	143	299	184	0 307	0 447	18 0	1 0151	0 195		4	IV

It has been demonstrated<sup>8</sup> that hypertrophy was proportional to protein (casein) consumption, and a formula expressing the relationship of protein consumption to kidney weight per unit of surface area was presented. MacKay and MacKay<sup>9</sup> and Wilson<sup>10</sup> recently observed that the degree of renal hypertrophy was influenced by the type of protein fed. In the present study the consumption of food was not measured, and the quantitative relationship between the intake of food and the size of the kidneys could not be made. Since the nitrogen content of the various meat and liver diets<sup>1b</sup> was not exactly the same, a comparison of the  $\frac{KW}{SA}$  ratios can best be made at the same nitrogen concentration of the two diets. The influence of liver and meat diets on the hypertrophy of the kidneys of the partially nephrectomized, unilaterally nephrectomized and intact control animals has been com-

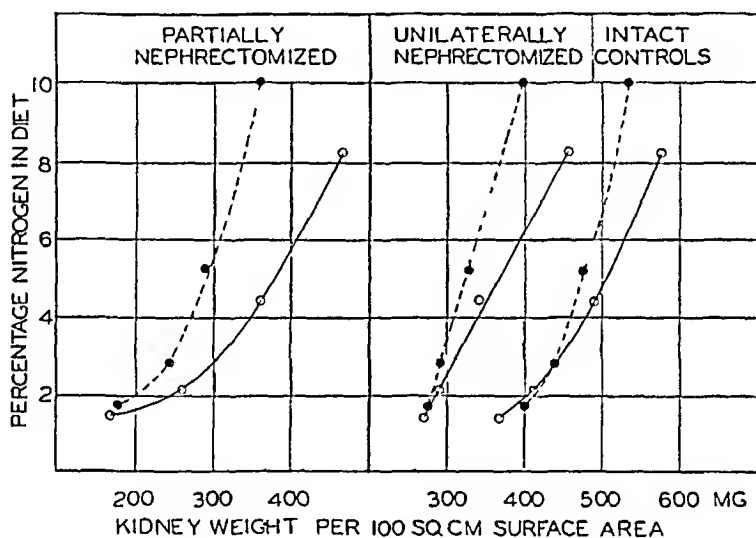


Chart 8—The influence of diets containing meat and liver on the  $\frac{KW}{SA}$  ratios of partially nephrectomized, unilaterally nephrectomized and intact rats. The broken line indicates the animals on diets containing meat. The solid line indicates those on diets containing liver.

pared in chart 8. With increasing amounts of protein, liver diets cause a progressively more marked hypertrophy, especially in the partially nephrectomized animals.

It has been shown by a number of workers that the urea ratio in normal human beings and animals is elevated immediately after the

8 MacKay, E. M., MacKay, L. L., and Addis, T. *Am. J. Physiol.* **86**: 459, 1928.

9 MacKay, E. M., and MacKay, L. L. *J. Nutrition* **8**: 187, 1934.

10 Wilson, H. E. C. *Biochem. J.* **27**: 1348, 1933.

ingestion of a meal containing protein<sup>11</sup> The maximal postprandial ratios were obtained in animals maintained on a meat diet<sup>12</sup> The lowest ratios were noted in human beings and animals on a low protein diet<sup>13</sup> In four cases of hemorrhagic Bright's disease, Keutmann and McCann<sup>14</sup> noted slight increases in the functional capacity of the kidney, as measured by urea clearance after a liberal protein intake Cope<sup>15</sup> found a depression of the clearance in persons with nephritis with normal or nearly normal function after lowering the basal protein intake Raising the protein intake of these patients had no consistent effect on the urea clearance In patients with depressed renal function, the clearance appeared to be fixed and was not appreciably influenced by the amount of protein fed Pitts<sup>12</sup> expressed the belief that the primary effect of protein on normal renal function is due to the action of amino-acids on glomerular activity Van Slyke and his co-workers<sup>16</sup> demonstrated that the urea clearance varied in direct proportion to renal blood flow In the present study, a quantitative relationship between the urea ratio and the amount of dietary protein has been shown for unilaterally nephrectomized and intact rats Continued ingestion of diets high in protein tends to decrease the ratio in partially nephrectomized animals No evidence is available to explain the changes in renal function due to the effect of diet

When an animal with a small remnant of kidney is given a diet containing a comparatively low percentage of protein (M 10 or L 10), the renal function is maintained at a fairly good level for a long time without the development of azotemia or of any marked degree of hypertension A small increase in the amount of nitrogen of the diet (M 20 or L 20) causes marked pathologic changes and loss of renal function Although the latter diets are considered to have protein concentrations which are minimal for the maintenance of intact rats, the reduced renal tissue of the partially nephrectomized rats seems to have reacted as to a definitely increased metabolic load The cause of this difference in animals ingesting additional small amounts of meat or liver is not

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11 (a) Addis, T, and Drury, D R *J Biol Chem* **55** 629, 1923 (b) Jolliffe, N, and Smith, H W *Am J Physiol* **99** 101, 1931 (c) Shannon, J A, Jolliffe, N, and Smith, H W *ibid* **101** 625, 1932 (d) Van Slyke, D D, Rhoads, C P, Hiller, A, and Alving, A Relationship of Urea Clearance to Renal Blood Flow, *ibid* **110** 387 (Dec) 1934

12 Pitts, R F *J Nutrition* **9** 657, 1935 Shannon and others<sup>11c</sup>

13 Goldring, W, Razinsky, L, Greenblatt, M, and Cohen, S *J Clin Investigation* **13** 743, 1934 Shannon and others<sup>11c</sup>

14 Keutmann, E H, and McCann, W S *J Clin Investigation* **11** 973, 1932

15 Cope, C L *J Clin Investigation* **12** 567, 1933

16 Van Slyke, D D, Rhoads, C P, Hiller, A, and Alving, A Relationships Between Urea Excretion, Renal Blood Flow, Renal Oxygen Consumption and Diuresis Mechanism of Urea Excretion, *Am J Physiol* **109** 336 (Aug) 1934

clear. Apparently the changes must be due either to the excretion of injurious products of protein breakdown, such as amino-acids,<sup>17</sup> to the effect of water-soluble nitrogenous extractives<sup>18</sup> or to the extra burden involved in the excretion of nitrogen metabolites per se.

The effects of diets high in protein on the kidneys of experimental animals has recently been reviewed.<sup>19</sup> The work of Newburgh and Curtis<sup>20</sup> is striking, since they reported renal damage when diets rich in liver, other meat and casein were fed to white rats with intact kidneys for a prolonged period. Liver produced the greatest damage in the shortest time, renal injury caused by other meat was not as marked and required a longer time for its production. It was believed these renal changes could be best explained by the differences in the amino-acid composition of the proteins fed. In a later report Newburgh and Johnston<sup>19</sup> postulated that the water-soluble extractives of liver and meat were responsible for the marked renal changes because when they fed sodium nucleate, pronounced renal damage was produced by comparatively small amounts of the material. After reduction of the renal tissue by unilateral nephrectomy, casein fed in high concentrations caused glomerular and tubular changes in a relatively short time.<sup>21</sup> Further reduction of renal tissue by partial nephrectomy caused pathologic changes very soon after operation in animals fed a standard diet containing 20 per cent of extracted meat.<sup>1a</sup> The effect of dietary protein on the kidney varies, therefore, with the type of protein fed and with the relative renal reserve.

In recent years attention has been called to the importance of feeding adequate amounts of protein to patients with certain types of renal disease.<sup>22</sup> It has been recognized that patients losing large amounts of protein in the urine must be fed relatively large amounts in an effort to maintain nitrogen equilibrium. Experimentation with animals has demonstrated that not only the quantity but the quality of protein foods is of importance in the production of renal injury. It has been shown, for example, that there is a great difference between the renal damage produced by diets rich in whole liver and that produced by liver washed free of water-soluble constituents.<sup>1b</sup> The qualitative aspects of protein

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17 Newburgh, L. H., and Marsh, P. L. Renal Injuries by Amino Acids, *Arch Int Med* **36** 682 (Nov.) 1925

18 Newburgh, L. H., and Johnston, M. W. *J Clin Investigation* **10** 153, 1931

19 Mitchell, H. H. *J Nutrition* **1** 271, 1929. Bischoff, Fritz *ibid* **5** 431, 1932

20 Newburgh, L. H., and Curtis, A. C. Production of Renal Injury in the White Rat by the Protein of the Diet, *Arch Int Med* **42** 801 (Dec.) 1928

21 Moise, T. S., and Smith, A. H. Effect of High Protein Diet on the Kidneys. Experimental Study, *Arch Path* **4** 530 (Oct.) 1927

22 Peters, J. P., Bulger, H. A., Lee, C. F., and Murphy, C. F. The Relation of Albuminuria to Protein Requirement in Nephritis, *Arch Int Med* **37** 153 (Feb.) 1926. Keutmann and McCann<sup>14</sup>

feeding must be stressed. Although protein per se may be a factor in producing renal lesions under strain, the nephrotoxic substances associated with protein foods must be seriously considered if there is any analogy between experimental animals and patients with renal lesions. Such factors as the amino-acid composition of the protein,<sup>15</sup> the non-protein constituents,<sup>19</sup> the products of purine metabolism<sup>18</sup> and the presence of excess phosphate precursors<sup>23</sup> and possibly of other substances may play an important rôle in the dietary regimen of the patient with disturbed renal function. Work in this laboratory is being continued with partially nephrectomized animals to determine the relationship between renal damage and the type of protein ingested.

#### SUMMARY

The effect of feeding diets containing various percentages (10, 20, 40 and 80) of whole dried meat to rats with intact kidneys and to unilaterally nephrectomized and partially nephrectomized rats has been studied.

The ingestion of these diets by intact and by unilaterally nephrectomized animals caused a progressive enlargement of the kidneys. When the kidneys of the rats on the M 10 diet were used as a standard, the degree of hypertrophy was the same for the control groups on both the M 20 and the M 40 diet. The kidneys of the animals on the M 80 diet showed a marked degree of hypertrophy, particularly in the unilaterally nephrectomized animals.

The syndrome in the partially nephrectomized rats was affected by the percentage of the whole meat in the diet in the following manner:

1 The frequency and the degree of hypertension became more pronounced as the content of whole meat in the diet was increased. A substantial relationship was demonstrated for the majority of the dietary groups between the blood pressure and the  $\frac{H}{S} \frac{W}{A}$  ratio.

2 A progressively increased volume of dilute urine was excreted during a concentration test as the percentage of meat in the diet was raised. This increased renal insufficiency was confirmed by a lowering of the urea ratio  $\frac{\text{urea excreted per hour}}{\text{urea in 100 cc of blood}}$ .

The pathologic changes were progressively exaggerated in the kidney remnant with the increase in the concentration of meat in the diet.

The average weight of the remnant of kidney increased with the increased concentration of meat and was accompanied by greater individual variations.

No immediate clinical application of these results can be made. The possible importance of the type of protein ingested by man and by animals with renal insufficiency has been considered.

# EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

## VI THE RELATION BETWEEN KIDNEY FUNCTION, KIDNEY WEIGHT AND SURFACE AREA IN INTACT AND UNILATERALLY NEPHRECTOMIZED RATS FED WHOLE DRIED MEAT DIETS

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AND

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The determination of the urea ratio,  $\frac{\text{urea in 1 hour's urine}}{\text{urea in 100 cc of blood}}$ , of Addis and his collaborators<sup>1</sup> has proved to be a satisfactory method for the estimation of the percentage of functioning renal tissue. It was found to be the best functional test to give an approximation of the quantitative and structural changes caused by unilateral nephrectomy<sup>2</sup> and by uranium "nephritis"<sup>3</sup>. The magnitude of the Addis ratio was found to be directly related to the size of the kidneys in intact rats,<sup>4</sup> in rabbits<sup>5</sup> and in human beings<sup>6</sup>. A relationship between the urea ratio and the surface area in the dog<sup>7</sup> and in man<sup>6</sup> has been demonstrated. It has also been shown that a relationship exists between the area of the body surface and kidney weight in the rat,<sup>8</sup> the rabbit,<sup>9</sup> the dog<sup>9</sup> and man<sup>6</sup>. It would appear that renal function, kidney weight

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This investigation was made possible by a grant from the National Live Stock and Meat Board and by the Edward N. Gibbs Prize Fund of the New York Academy of Medicine

1 (a) Addis, T., and Watanabe, C. K. *J. Biol. Chem.* **28** 251, 1916 (b) Addis, T. *J. Urol.* **1** 253, 1917, (c) Renal Function and the Amount of Functioning Tissue, *Arch. Int. Med.* **30** 378 (Sept.) 1922

2 Addis, T., Myers, B. A., and Oliver, J. The Regulation of Renal Activity, *Arch. Int. Med.* **34** 243 (Aug.) 1924

3 Watanabe, C. K., Oliver, J., and Addis, T. *J. Exper. Med.* **28** 359 (Sept.) 1918

4 MacKay, E. M., and Raulston, B. O. *J. Exper. Med.* **53** 109, 1931

5 Taylor, F. B., Drury, D. R., and Addis, T. *Am. J. Physiol.* **65** 55, 1923

6 MacKay, E. M. Kidney Weight, Body Size and Renal Function, *Arch. Int. Med.* **50**:590 (Oct.) 1932

7 Rhoads, C. P., Alving, A. S., Hiller, A., and Van Slyke, D. D. *Am. J. Physiol.* **109** 329, 1934

8 MacKay, L. L., and MacKay, E. M. *Am. J. Physiol.* **83** 191, 1927

9 Stewart, J. N. *Am. J. Physiol.* **58** 45, 1921

and body surface are all directly related to one another in man and in experimental animals. The aforementioned experiments have been performed on both intact and unilaterally nephrectomized animals maintained on standard diets. It is our purpose in this paper to consider the effect of dietary changes on the  $\frac{\text{urea ratio}}{\text{kidney weight}}$ ,  $\frac{\text{kidney weight}}{\text{surface area}}$  and  $\frac{\text{urea ratio}}{\text{surface area}}$  ratios in intact and in unilaterally nephrectomized rats.

This study was based on an analysis of part of the data already presented<sup>10</sup>. Only animals on which complete data were available were included in the present analysis, and hence the average figures are not identical with the figures previously reported<sup>10</sup>. The experimental procedures, experimental diets and abbreviations were outlined<sup>10</sup>.

### RESULTS

*Intact Animals*—The  $\frac{K}{S} \frac{W}{A}$  ratio, kidney weight, surface area, Addis ratio,  $\frac{\text{urea ratio}}{\text{kidney weight}}$  ratio and  $\frac{\text{urea ratio}}{\text{surface area}}$  ratios obtained in the intact rats on diets containing percentages of various whole meat are presented in table 1. It will be seen that the average urea ratio and the average kidney weight per hundred square centimeters of body surface increased with the greater percentage of whole meat in the diet. It is significant that almost identical average values for the urea ratio per gram of kidney tissue (36.3, 36.9, 35.6 and 37.6) were obtained in these animals on diets containing, respectively, 10, 20, 40 and 80 per cent of whole dried meat. The respective average urea ratios per hundred square centimeters of body surface for the dietary groups were 0.144, 0.158, 0.184 and 0.206, which with the ratio for the group receiving the M10 diet as unity represents a proportion of 1, 1.08, 1.20 and 1.32, respectively. In a similar manner the proportionate increase in the  $\frac{K}{S} \frac{W}{A}$  ratios was 1, 1.10, 1.28 and 1.43 for the respective diets.

*Unilaterally Nephrectomized Animals*—The data for the individual unilaterally nephrectomized rats are presented in table 2. The average values for the urea ratio per gram of kidney tissue were 38.3, 40.7, 36.6 and 36 for the respective dietary groups. The respective average urea ratios per hundred square centimeters of body surface for these groups were 0.111, 0.119, 0.126 and 0.145, which represent a proportion of 1, 1.07, 1.13 and 1.31. In a similar manner the proportionate increase in the  $\frac{K}{S} \frac{W}{A}$  ratios was 1, 1, 1.17 and 1.37, respectively.

<sup>10</sup> Chanutin, A., and Ludewig, S. Experimental Renal Insufficiency Produced by Partial Nephrectomy. V. Diets Containing Whole Dried Meat, Arch Int Med, this issue, p. 60.

TABLE 1—*Observations on Intact Rats*

Rat	Duration of Experiment, Days	Kidney Weight	Kidney Weight, Gm	Urea Ratio	Surface Area, Sq Cm	Urea Ratio	Urea Ratio
		Surface Area $\times 100$		Blood Con- centration $\times 100$		Kidney Weight	Surface Area
M 10							
1	44	0 425	1 514	50	356	33 0	0 141
2	44	0 430	1 697	61	386	36 0	0 158
3	44	0 419	1 456	60	348	41 2	0 172
4	44	0 360	1 083	62	302	57 1	0 205
5	44	0 374	1 056	55	283	52 0	0 193
6	44	0 382	1 126	50	295	44 5	0 170
7	44	0 383	1 237	43	323	34 8	0 133
8	44	0 408	1 401	70	343	50 0	0 204
9	59	0 424	1 602	65	379	40 5	0 172
10	59	0 380	1 275	48	336	37 6	0 143
11	59	0 444	1 571	36	354	22 9	0 102
12	61	0 482	1 749	28	362	16 0	0 077
13	61	0 495	1 753	34	354	19 3	0 096
14	61	0 433	1 369	47	316	34 4	0 149
15	61	0 425	1 637	58	386	35 4	0 150
16	142	0 344	1 016	44	295	43 3	0 149
17	146	0 342	1 350	34	396	25 2	0 086
18	147	0 377	1 405	38	373	26 2	0 102
19	155	0 368	1 509	38	412	27 0	0 092
20	203	0 453	1 886	69	415	36 6	0 166
21	203	0 328	1 138	48	345	42 2	0 139
22	226	0 394	1 340	59	340	44 0	0 173
Average		0 403		50		36 3	0 144
M 20							
23	37	0 392	1 121	54	286	48 0	0 188
24	37	0 388	1 191	52	307	43 6	0 169
25	37	0 468	1 702	60	364	35 2	0 165
26	37	0 435	1 613	60	370	37 2	0 162
27	37	0 393	1 179	59	300	50 0	0 197
28	37	0 483	1 810	67	375	37 0	0 179
29	37	0 492	1 850	48	376	25 9	0 128
30	52	0 483	1 803	55	374	30 4	0 147
31	52	0 550	2 018	63	366	31 2	0 173
32	52	0 499	1 995	80	400	40 0	0 200
33	52	0 469	1 689	53	300	31 4	0 177
34	52	0 426	1 839	53	386	28 8	0 137
35	105	0 485	2 017	62	415	30 8	0 150
36	118	0 412	1 494	35	364	23 4	0 096
37	122	0 252	1 117	74	442	66 3	0 168
38	146	0 350	1 080	51	308	47 2	0 165
39	153	0 418	1 439	43	344	29 9	0 125
40	178	0 368	1 252	51	340	40 7	0 150
41	183	0 472	1 934	75	410	38 8	0 183
42	207	0 472	2 265	79	478	34 8	0 165
43	207	0 434	1 620	42	373	25 9	0 113
44	217	0 422	1 735	60	412	34 6	0 146
Average		0 435		58		36 9	0 158
M 40							
45	38	0 478	1 786	67	374	37 5	0 179
46	38	0 470	1 680	61	358	36 3	0 171
47	38	0 439	1 240	42	283	33 8	0 148
48	38	0 515	2 013	64	391	31 8	0 164
49	38	0 535	2 096	74	392	35 3	0 188
50	38	0 506	1 921	76	380	39 5	0 200
51	38	0 502	1 778	57	354	32 1	0 161
52	53	0 628	2 334	67	286	28 7	0 178
53	53	0 541	2 089	74	300	35 4	0 246
54	53	0 573	2 173	82	294	37 7	0 278
55	53	0 469	1 392	62	194	44 6	0 520
56	66	0 390	1 135	30	291	26 4	0 103
57	84	0 430	1 588	54	369	34 1	0 147
58	134	0 350	1 167	48	333	41 2	0 144
59	141	0 470	1 870	67	398	35 8	0 168
60	149	0 435	1 785	60	410	33 6	0 146
Average		0 483		62		35 2	0 184



TABLE 1—*Observations on Intact Rats—Continued*

Rat	Duration of Experiment, Days	Kidney Weight	Kidney Weight, Gm	Urea Ratio Urine Rate	Surface Area, Sq Cm	Urea Ratio	Urea Ratio
		Surface Area × 100		Blood Concentration × 100		Kidney Weight	Surface Area
				M 80			
61	38	0 545	1 630	59	297	36 2	0 198
62	38	0 570	2 072	70	362	33 8	0 193
63	38	0 544	1 587	56	292	35 3	0 143
64	38	0 495	1 492	82	302	54 9	0 211
65	38	0 615	2 261	61	368	27 0	0 166
66	38	0 648	1 886	103	291	54 7	0 354
67	53	0 550	1 997	69	364	34 6	0 189
68	53	0 535	1 590	67	297	42 2	0 226
69	53	0 630	2 520	64	402	25 4	0 159
70	53	0 602	2 255	96	374	42 5	0 256
71	53	0 600	2 067	87	345	42 0	0 252
72	53	0 530	1 595	63	302	39 5	0 208
73	53	0 610	2 105	81	346	40 3	0 234
74	64	0 532	1 810	47	341	25 9	0 138
75	115	0 555	1 702	60	307	35 2	0 196
76	120	0 532	2 135	84	402	39 4	0 209
77	161	0 510	1 555	75	304	48 2	0 247
78	191	0 537	1 716	51	320	29 7	0 159
79	203	0 547	2 170	83	397	38 2	0 209
80	203	0 485	1 620	61	334	37 6	0 183
81	377	0 530	1 712	47	323	27 4	0 145
Average		0 533		69		37 6	0 206

TABLE 2—*Observations on Unilaterally Nephrectomized Rats*

Rat	Duration of Experiment, Days	Kidney Weight	Kidney Weight, Gm	Urea Ratio Urine Rate	Surface Area, Sq Cm	Urea Ratio	Urea Ratio
		Surface Area × 100		Blood Concentration × 100		Kidney Weight	Surface Area
				M 10			
1	35	0 278	0 934	38	336	40 7	0 113
2	35	0 270	0 901	36	334	39 9	0 108
3	35	0 240	0 680	27	253	39 7	0 095
4	35	0 277	0 868	35	313	40 3	0 112
5	35	0 300	1 084	35	362	32 2	0 097
6	50	0 295	1 093	33	370	30 2	0 089
7	50	0 378	1 116	47	376	42 2	0 125
8	50	0 316	1 195	43	379	36 0	0 113
9	50	0 354	1 074	46	304	42 8	0 151
10	50	0 300	1 115	52	372	46 7	0 140
11	50	0 276	0 756	32	274	42 3	0 117
12	101	0 327	1 125	41	345	36 4	0 119
13	142	0 264	0 724	31	274	42 8	0 113
14	142	0 300	0 870	42	239	48 3	0 145
15	146	0 238	1 020	33	428	32 4	0 077
16	147	0 264	0 830	23	314	27 7	0 073
17	152	0 322	1 254	38	359	30 1	0 098
Average		0 294		37		38 3	0 111
				M 20			
18	35	0 274	0 838	51	306	61 0	0 167
19	35	0 239	0 865	34	299	39 3	0 114
20	35	0 332	1 381	43	417	31 1	0 108
21	35	0 332	1 244	43	375	34 6	0 115
22	35	0 314	1 250	54	398	43 3	0 136
23	35	0 308	1 095	40	356	36 5	0 112
24	35	0 288	0 991	35	345	35 3	0 102
25	50	0 306	1 149	38	376	33 0	0 101
26	50	0 323	1 200	45	366	37 5	0 123
27	50	0 264	0 797	42	302	52 7	0 139
28	50	0 263	0 794	37	302	46 6	0 123
29	50	0 277	0 842	38	304	45 1	0 125
30	90	0 320	1 252	50	392	39 9	0 123
31	105	0 332	1 245	35	376	27 1	0 093
32	113	0 252	0 734	29	291	39 6	0 092
33	120	0 254	0 803	40	305	50 0	0 131
34	154	0 324	1 468	59	453	40 3	0 130
35	166	0 304	1 300	65	428	50 0	0 152
36	166	0 291	1 200	50	413	41 7	0 121
37	202	0 270	0 941	35	348	37 0	0 101
38	207	0 288	0 985	32	341	32 5	0 094
Average		0 295		42		40 7	0 119

TABLE 2—*Observations on Unilaterally Nephrectomized Rats—Continued*

Rat	Duration of Experiment, Days	Kidney Weight	Kidney Weight, Gm	Urea Ratio Urine Rate	Surface Area, Sq Cm	Urea Ratio	Urea Ratio
		Surface Area × 100		Blood Con- centration × 100		Kidney Weight	Surface Area
M 40							
39	41	0 378	1 484	45	392	30 3	0 115
40	41	0 370	1 310	46	354	35 0	0 130
41	41	0 316	0 906	38	286	42 0	0 138
42	41	0 372	1 327	55	356	41 5	0 154
43	41	0 368	1 229	50	334	40 7	0 150
44	41	0 314	0 805	28	256	34 8	0 110
45	41	0 374	1 303	46	348	35 2	0 132
46	43	0 346	0 950	38	274	40 0	0 139
47	43	0 352	0 976	33	277	33 8	0 119
48	43	0 370	1 310	55	354	42 0	0 155
49	66	0 327	1 200	43	366	35 8	0 118
50	84	0 338	1 392	45	412	32 3	0 109
51	84	0 362	1 333	51	370	38 2	0 138
52	129	0 303	1 180	36	390	30 5	0 092
53	134	0 340	1 405	50	413	35 6	0 121
54	176	0 264	0 770	30	292	39 0	0 103
Average		0 343		43		36 6	0 126
M 80							
55	41	0 334	0 863	33	258	38 2	0 128
56	41	0 418	1 425	59	341	41 3	0 173
57	41	0 347	0 923	40	266	43 3	0 150
58	41	0 385	1 032	36	268	34 8	0 134
59	43	0 435	1 513	48	348	31 7	0 138
60	43	0 435	1 633	51	376	31 2	0 135
61	43	0 418	1 376	66	318	48 0	0 208
62	43	0 405	1 363	71	334	52 0	0 212
63	43	0 432	1 160	47	268	40 5	0 175
64	43	0 430	1 410	54	328	38 3	0 164
65	43	0 465	1 580	70	340	44 2	0 206
66	43	0 474	1 615	55	341	34 1	0 162
67	70	0 428	1 622	61	379	37 6	0 161
68	87	0 447	1 733	46	389	26 6	0 118
69	87	0 361	1 184	23	328	19 4	0 070
70	121	0 427	1 685	46	397	27 3	0 116
71	143	0 386	1 462	42	379	28 7	0 111
72	161	0 328	1 029	39	313	38 0	0 125
73	162	0 387	1 074	31	278	28 8	0 111
74	203	0 358	1 219	50	339	41 0	0 147
75	203	0 364	1 219	54	333	44 3	0 162
76	225	0 382	1 170	27	306	23 1	0 088
Average		0 402		48		36 0	0 145

## COMMENT

It is striking that almost identical average values for the urea ratio per gram of kidney tissue were obtained for all eight groups of rats studied. The average values for the  $\frac{\text{urea ratio}}{\text{kidney weight}}$  ratio were 36.5 and 37.9 for all the intact and all the unilaterally nephrectomized rats, respectively. Because of the close relationship between the kidney weight and the urea ratio in the animals with one and two kidneys, the data for both groups were combined and presented diagrammatically in chart 1. The percentage of the mean normal value for the urea ratio was calculated for the dietary groups from the average ratio obtained in the intact animals of the respective group. The statistical reliability of these  $\frac{\text{urea ratio}}{\text{kidney weight}}$  ratios for the various dietary groups was obtained by determining the correlation coefficients and the probable errors as follows: M10,  $0.41 \pm 0.089$ , M20,  $0.69 \pm 0.053$ , M40,  $0.86 \pm 0.030$ , and M80,  $0.65 \pm 0.059$ . There is a high relationship for

the group receiving the M40 diet, a marked relationship for the groups receiving the M20 and M80 diets and a low correlation for the group on the M10 diet. These findings indicate that the variation or constancy of the urea ratio per unit of kidney weight is dependent on the protein intake.

MacKay and Raulston<sup>4</sup> demonstrated a constant urea ratio per gram of kidney tissue in intact normal rats of different ages and sizes fed a

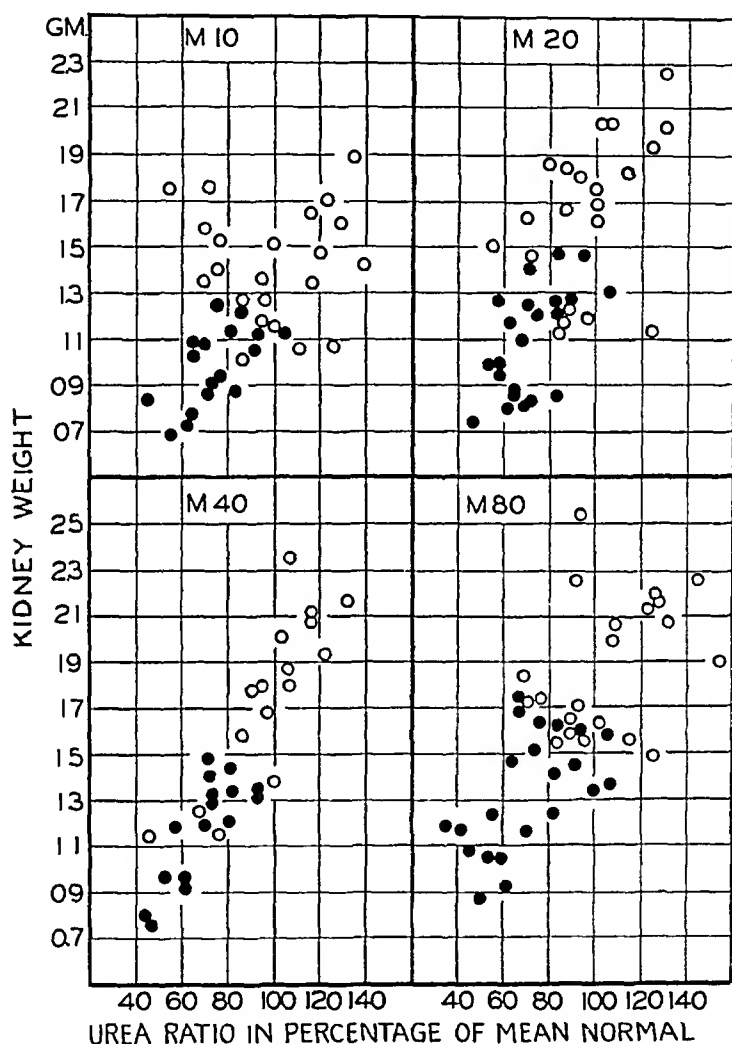


Chart 1—Relation between kidney weight and urea (Addis) ratio. In charts 1 and 2 the unshaded circles indicate rats with both kidneys intact, and the shaded circles indicate those with only one kidney.

standard diet. This finding has been confirmed and extended to show that this relationship is constant despite the effect of diet on renal hypertrophy on the animals with one and two kidneys. From the data given in the previous paper,<sup>10</sup> it can be seen that the partially nephrectomized rats in which renal damage developed show absolutely no constancy in this relationship.

It has been demonstrated that there is a direct relationship between the kidney weight and the surface area in intact rats on a standard diet<sup>8</sup> It is obvious from chart 2 that this has been confirmed for rats with two kidneys on a nitrogen intake similar to that obtained from the standard diet In addition it can be seen that there is a direct rela-

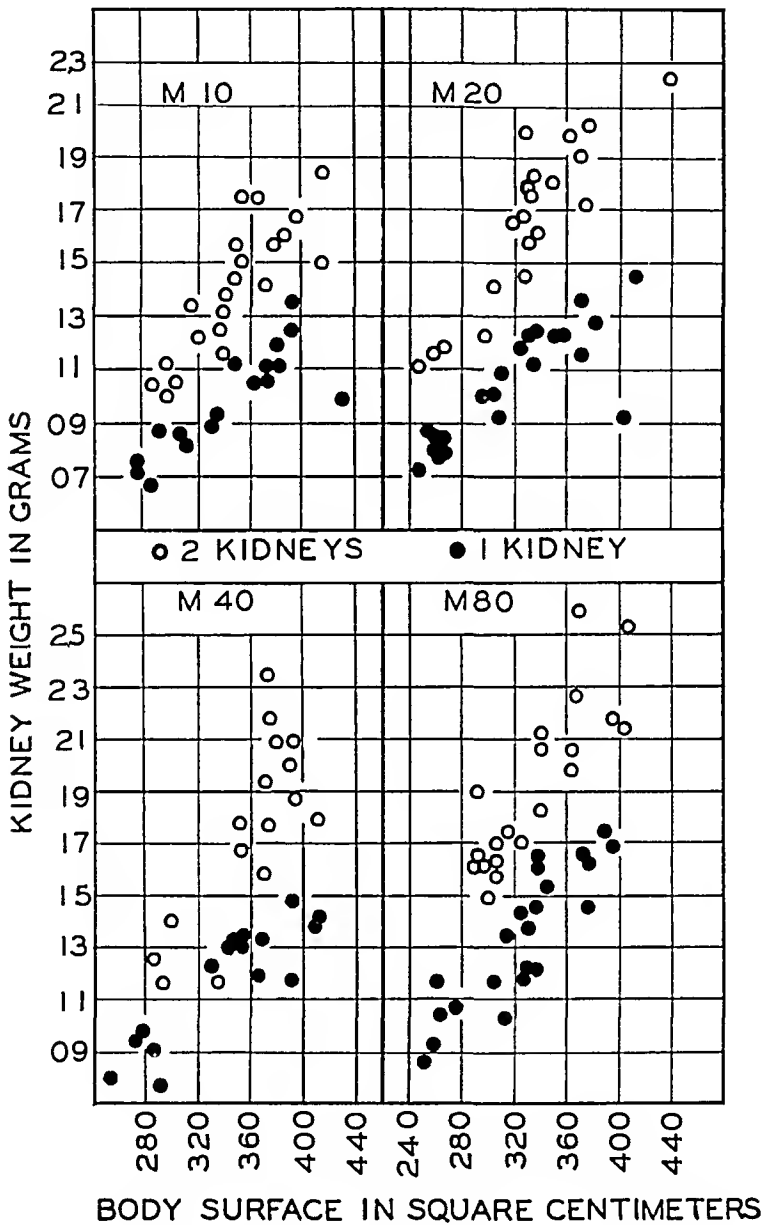


Chart 2—The relation of kidney weight to surface area

tionship for all diets but the ratios are not the same Furthermore, there is the same kind of direct relationship for the unilaterally nephrectomized animals, but in these rats a unit of kidney weight corresponds to a greater surface area

The direct relation of renal function to body surface and kidney weight in man and in animals has been reviewed by MacKay<sup>6</sup> In

the present paper, it is shown that the urea ratio is proportional to the surface area if the degree of renal hypertrophy is considered. In the rat, therefore, one cannot use body surface as an index of renal function unless a factor is used which makes allowance for the dietary regimen. It is reasonable to assume that this holds true for other experimental animals and for man.

#### SUMMARY

The relation between kidney weight, surface area and the urea (Addis) ratio,  $\frac{\text{urea excreted per hour}}{\text{urea in 100 cc of blood}}$ , was compared in intact and unilaterally nephrectomized rats fed diets containing 10, 20, 40 and 80 per cent of whole dried meat.

It was shown that the weight of the kidneys is directly related to the surface area in the animals ingesting diets containing different concentrations of protein.

The ratio  $\frac{\text{urea ratio}}{\text{kidney weight}}$  is constant for these animals on all dietary groups. The highest degree of correlation for this ratio was found in the group ingesting 40 per cent of whole meat.

The values for the  $\frac{\text{urea ratio}}{\text{surface area}}$  ratio increased in both the intact and the unilaterally nephrectomized animals with the added increments of whole meat in the diet. These values were proportional to the degree of renal hypertrophy. Renal function can be estimated in these animals provided the urea ratio for a given diet is known.

# EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

## VII THE RELATIONSHIP OF URINE UREA, BLOOD UREA AND UREA (ADDIS) RATIO IN RATS ON WHOLE DRIED MEAT DIETS

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AND

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The present study deals with the effect of feeding diets containing various concentrations of whole meat on the amount of urea in the urine and blood and the urea (Addis) ratio,  $\frac{\text{urea excreted}}{\text{blood urea}}$  in partially nephrectomized, unilaterally nephrectomized and intact rats

The experimental procedure, the experimental diets and abbreviations were outlined in a previous paper<sup>1</sup> The data for all animals excreting less than 50 per cent of the urea solution administered were excluded The previous data have been supplemented by values obtained at frequent intervals in individual animals

### RESULTS

The effect of various concentrations of whole dried meat on the amount of urea in the blood and urine and on the urea ratio,  $\frac{\text{urea excreted per hour}}{\text{urea in 100 cc blood}} \times 100$ , of partially nephrectomized and control animals (unilaterally nephrectomized and intact) is shown in chart 1 Five phases of renal function are indicated by the oblique lines, representing calculated urea ratios of 5, 10, 15, 20 and 60, which are indicative of stages from severe renal insufficiency to normal function It can be seen that among the partially nephrectomized rats the percentage incidence of marked renal insufficiency in the group receiving the M 80 diet

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From the Laboratory of Physiological Chemistry, the University of Virginia  
This investigation was made possible by a grant from the National Live Stock and Meat Board and by the Edward N Gibbs Prize Fund of the New York Academy of Medicine

The statistical analyses were performed by Dr Williams, who is on the staff of the Leander McCormick Observatory

1 Chanutin, A, and Ludewig, S Experimental Renal Insufficiency Produced by Partial Nephrectomy V Diets Containing Whole Dried Meat, Arch Int Med, this issue, p 60

is four times as great as that in the group on the M 10 diet and, conversely, the percentage of cases in which the ratio was above 20 is greater for the animals receiving lower protein diets

An unadjusted and an adjusted curve are shown on the diagrams of the groups on the M 20, M 40 and M 80 diets, these two curves are identical for the group on the M 10 diet Each unadjusted curve has been drawn midway between the two regression curves obtained in the standard statistical manner for the particular group

From the dispersion of the individual points around the curve, it was found that in the case of the animals on the M 10 diet the probable

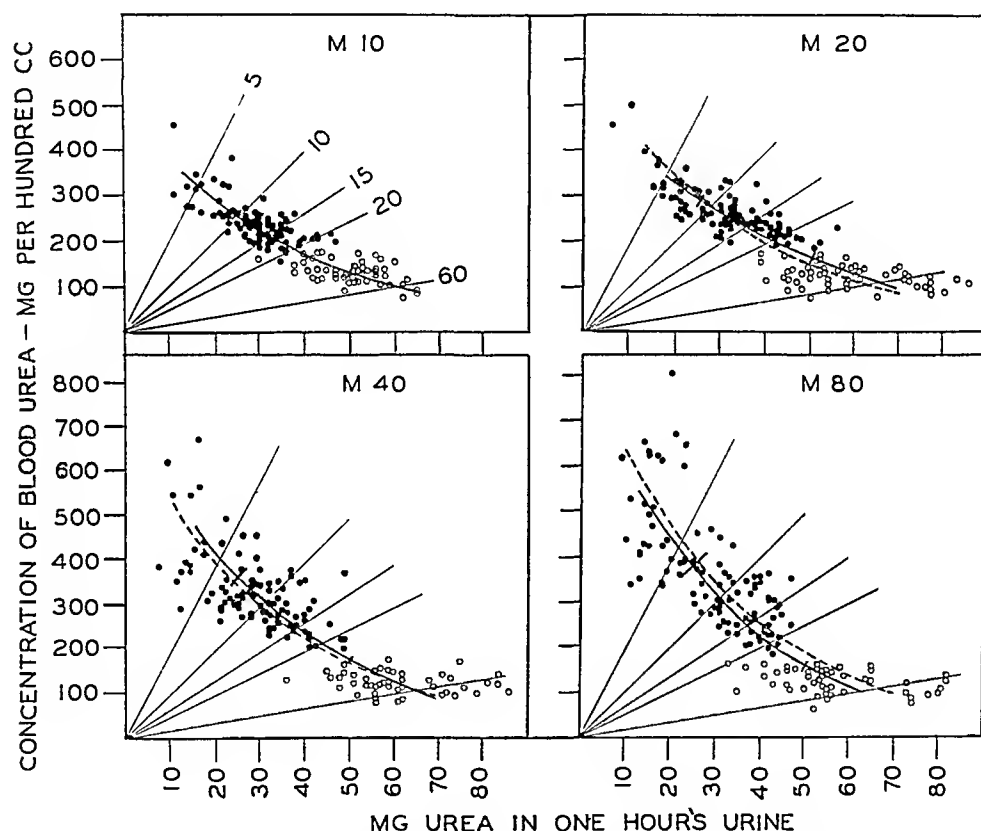


Chart 1—The relation of blood urea and urine urea in partially nephrectomized, intact and unilaterally nephrectomized rats The oblique lines represent the urea ratio,  $\frac{\text{urea excreted}}{\text{blood urea}} \times 100$  The solid dots represent values for partially nephrectomized rats, and the open circles, values for control animals

error of a single point is 4.5 units parallel to the x axis (urine urea) In other words, half of the values observed lie within 4.5 units of the curve in the x direction In the direction of the y axis (blood urea) the probable error varies from about 14 units at y equals 100 to 40 units at y equals 300 The scatter of the points around the curve for the animals on M 20 diet is only slightly greater, but for the group on the M 40 diet it is considerably greater The greatest scatter is seen in the

group on the M 80 diet, in which the probable error of a single point in the  $x$  direction is 5 units at the urine urea concentration of 50 and 75 units at the value of 20. In the direction of the  $y$  axis, the probable error varies from 20 units at  $y$  equals 100 to 90 units at  $y$  equals 500.

The four unadjusted curves show progressive changes in position. The large number of points defining each curve makes the probable error of the position of each curve very small. The probable error for the animals on the M 10 diet is smallest, and that for the animals on the M 80 diet is largest. The two heavy bars perpendicular to each of the four unadjusted curves give a measure of the accuracy of the position of the curves. The bars extend to three times the probable error on each side of the curve, thus giving odds of 20:1 that the true curve lies within a zone defined by the tips of the bars. Furthermore, the odds are 5:1 that the true curve lies within a zone two-thirds this width. The unadjusted curve for the M 80 data was drawn with strict reference to the regression points, but the position was not correctly represented at the lower end, since there was scarcity of points at  $y$  equals 200. The position of the curves at these points for rats on other diets is more accurate. Hence the reliability of the relative positions of the curves cannot be questioned, with the exception of the systematic error noted in the curve for animals with the M 80 diet.

To represent the trend more clearly and to correct for the systematic error of the lower end of the M 80 curve, adjusted curves have been adopted (chart 2), which are probably closer to the true picture. Since the shape of each of the unadjusted curves was practically exponential, the adjusted curves are also exponential, the formulas being given on the chart. The significance of these curves is evident when the values for urea in the blood and in the urine are compared on the same oblique line which represents urea ratios. The absolute amount of urea excreted is related to the degree of renal insufficiency. In animals with normal renal function with ratios of 60, it is seen that the diet has little effect on the urea concentration of the blood and urine. However, when renal function is decreased to a urea ratio of 5, it can be seen that the value for urine urea is increased from 16 to 21 and that the value for the blood urea is increased from 320 to 420 owing to the respective effects of the M 10 and M 80 diets. The differences in the amount of urea excreted by the animals on the various diets at any given urea ratio appear to be significant. Thus it is seen that the dietary regimen is important in its influence on the factors which determine the urea ratio.

The curves in chart 3 represent an analysis of the effect of diet on the concentration of urea in the blood at any given urea ratio in percentage of the mean normal. The exponential equations for the adjusted



curves for urea in the blood and urine were transformed into the equations which gave the relation between the blood urea content and the percentage urea ratio. The curves presented were drawn from these derived formulas. It can be seen that the concentration of blood urea is not affected by diet at any given urea ratio until severe renal insufficiency is encountered. For practical purposes, the differences in

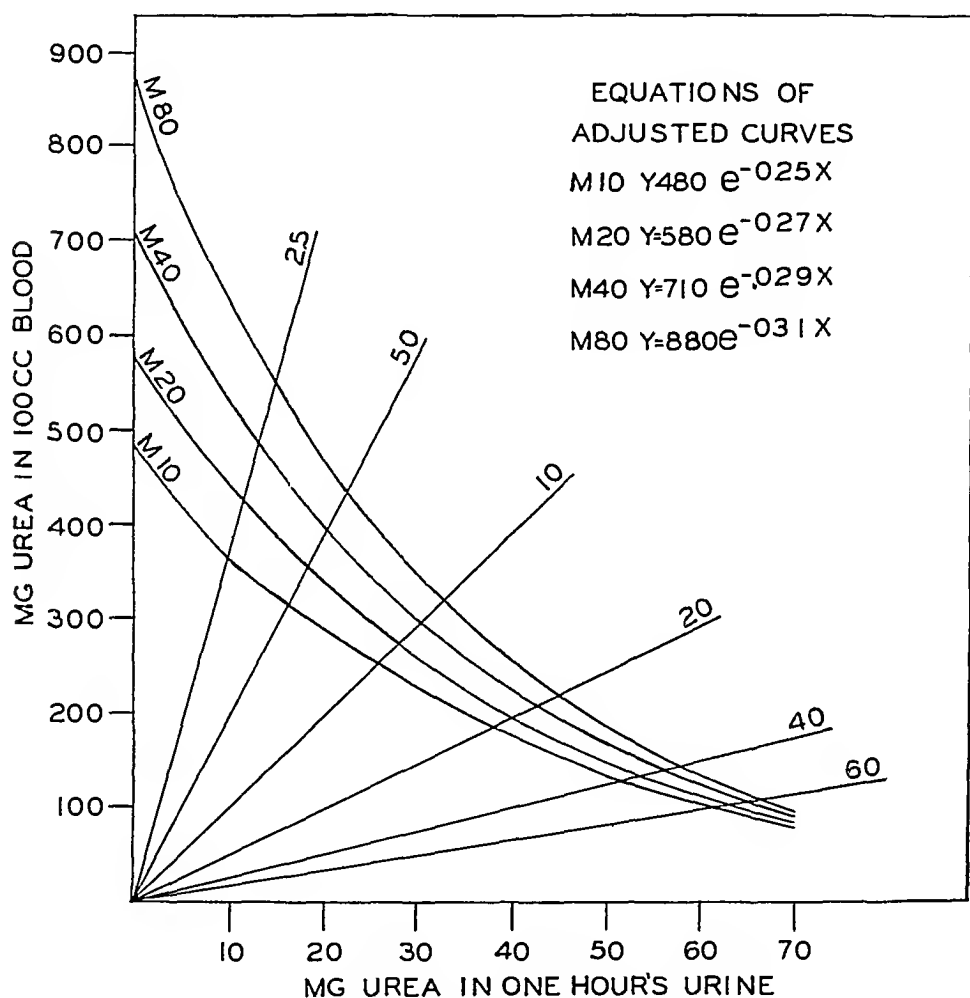


Chart 2—The relation of the adjusted curves for blood urea and urine urea

the blood values at any given urea ratio expressed in percentage of the mean normal value are not significant.

MacKay and Rytand<sup>2</sup> expressed the relation of the blood urea concentration to the Addis ratio in patients with Bright's disease in the form of a rectangular hyperbola ( $xy=k$ ). Since similar analyses in partially nephrectomized rats had yielded exponential equations, their

<sup>2</sup> MacKay, E. M., and Rytand, D. A. Significance of the Phenolsulphonphthalein Test of Renal Function, *Arch Int Med* 55 131 (Jan) 1935

data were recalculated. The values for urea in the urine and blood were obtained from table 3 of MacKay and Ryland's paper, and a mean curve was derived from two regression curves. This curve was readily fitted by an exponential equation, which was transformed into the equation given in chart 3 to express the relation between the concentration of blood urea and the Addis ratio. When the curve corresponding to this equation was drawn on the figure given in MacKay and Ryland's paper, it was found to lie satisfactorily between the two sets

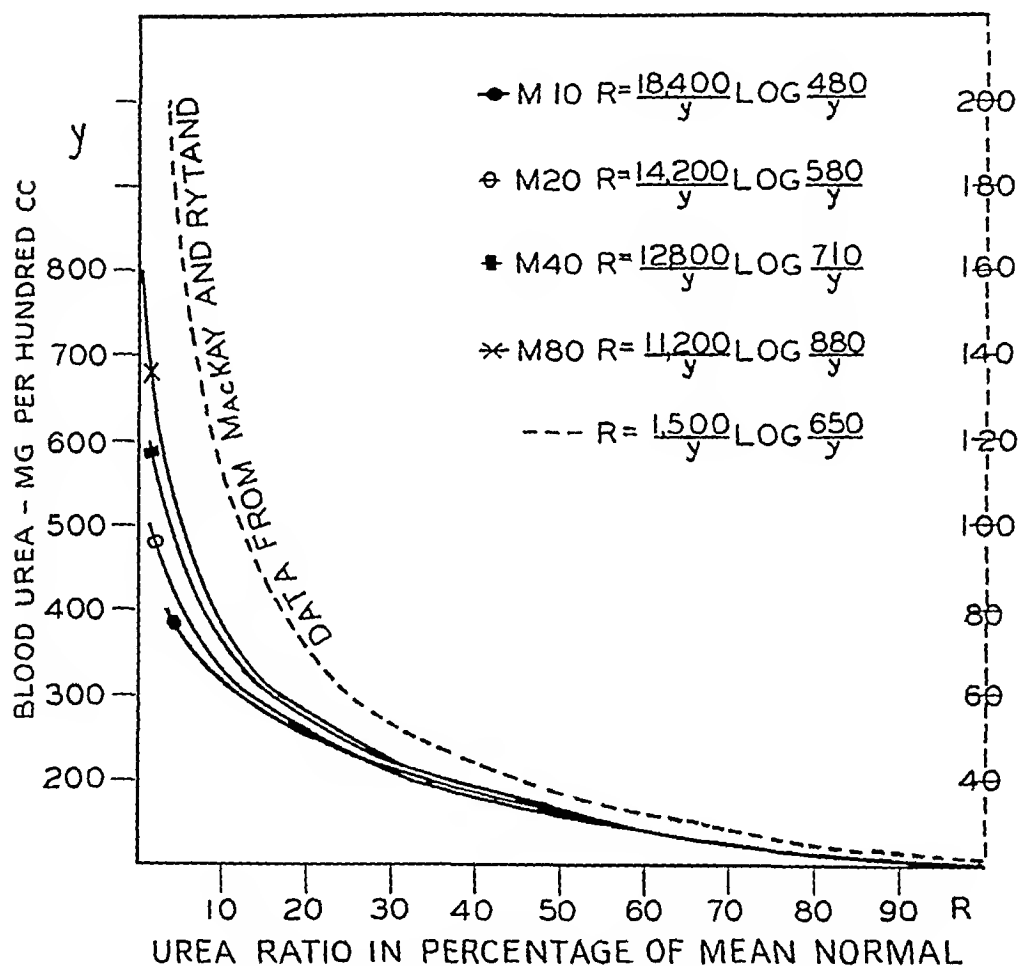


Chart 3—The relation between the blood urea concentration and the urea ratio in percentage of the mean normal value

of points computed by these authors, but it did not correspond to the rectangular hyperbola presented. It can be seen in chart 3 that the shape of the curve obtained for nephritic patients is similar to that for experimental animals.

#### SUMMARY

The effect of diets containing 10, 20, 40 and 80 per cent of whole dried meat on the amount of urea in the blood and urine of rats with

renal function varying from normal to marked renal insufficiency has been investigated. The positions of the exponential curves derived from the data showed that the concentration of urea in the blood and in the urine at any given urea ratio was greater the higher the protein intake. The differences were progressively more marked with increased renal insufficiency.

A comparison of the blood urea concentration and the urea ratio expressed in percentage of the mean normal value indicated that diet has no effect on this relationship until severe renal insufficiency develops.

# EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

## VIII COMPARISON OF THE UREA (ADDIS) RATIO WITH RESULTS OF OTHER TESTS OF RENAL FUNCTION

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AND

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Our purpose in this paper is to compare the blood urea concentration and blood pressure and the specific gravity, volume and protein content of urine collected during a concentration test with the urea ratio in partially nephrectomized rats fed diets containing different amounts of whole dried meat. In recent years the urea clearance has been compared with the concentration of urea,<sup>1</sup> and of creatinine<sup>1b</sup> in the blood, hemoglobin content,<sup>1b</sup> phenolsulfonphthalein excretion,<sup>1b, c</sup> urinary specific gravity<sup>2</sup> and  $\frac{\text{urea nitrogen}}{\text{nonprotein nitrogen}}$ <sup>3</sup> ratio. In the experiments reported by Addis<sup>4</sup> and Van Slyke<sup>5</sup> the ability of the kidneys to excrete urea appeared to be the most sensitive indicator of the state of renal function.

### RESULTS

*Blood Urea*—MacKay and MacKay<sup>1a</sup> and Van Slyke and his co-workers<sup>1b</sup> found that the urea concentration of the blood did not rise appreciably until the active kidney tissue was reduced one-half as measured by the urea clearance in patients with Bright's disease. As

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From the Laboratory of Physiological Chemistry, the University of Virginia.

This investigation was made possible by a grant from the National Live Stock and Meat Board and by the Edward N. Gibbs Prize Fund of the New York Academy of Medicine.

1 (a) MacKay, E. M., and MacKay, L. L. *J. Clin. Investigation* **4** 127, 1927. (b) Van Slyke, D. D., McIntosh, J. F., Moller, E., Hannon, R. R., and Johnston, C. *ibid.* **8** 357, 1930. (c) MacKay, E. M., and Rytand, D. A. Significance of the Phenolsulphonphthalein Test of Renal Function, *Arch. Int. Med.* **55** 131 (Jan.) 1935.

2 Alving, A. S., and Van Slyke, D. D. *J. Clin. Investigation* **13** 969, 1934.

3 Mosenthal, H. O., and Bruger, M. The Urea Ratio as a Measure of Renal Function, *Arch. Int. Med.* **55** 411 (March) 1935.

4 Addis, T. *Am. J. M. Sc.* **176** 624, 1928.

5 Van Slyke, D. D., Stillman, E., Moller, E., Ehrlich, W., McIntosh, J. F., Leiter, L., MacKay, E. M., Hannon, R. R., Moore, N. S., and Johnston, C. *Medicine* **9** 257, 1930.

the renal damage progressed from this point, the value for blood urea continued to become elevated MacKay and Rytand<sup>1c</sup> made a statistical study of the relationship of the concentration of blood urea to renal function in patients with nephritis

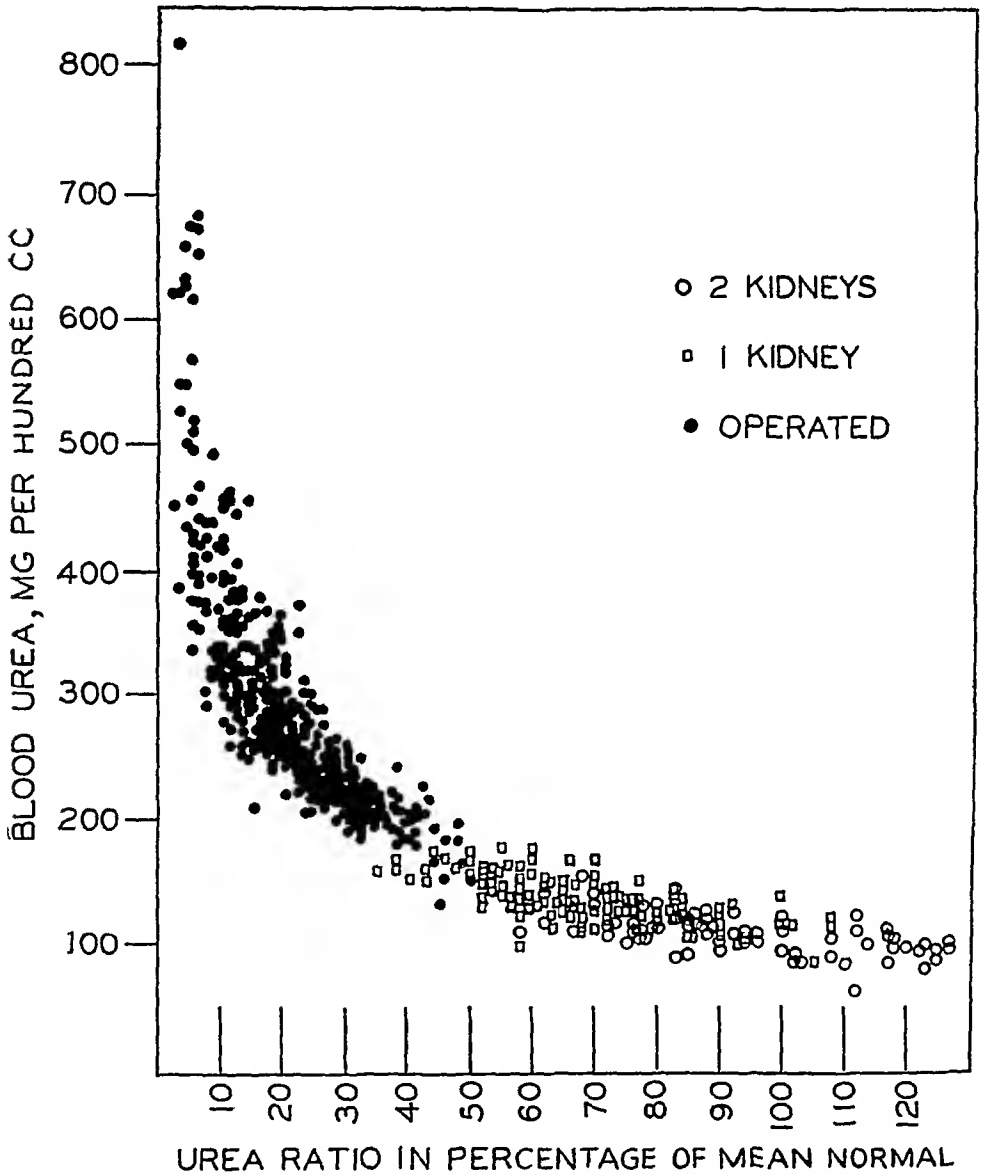


Chart 1—The relation between the Addis ratio (percentage of normal) and the blood urea concentration

In chart 1 the scatter point distribution of all values for blood urea and urea ratio in percentage of the mean normal values for all animals is presented It can be seen that the lower limits for the urea ratio for the unilaterally nephrectomized rats and for the intact rats were about 40 and 60, respectively, and that the highest values for the partially nephrectomized rats were about 50 As the values for the urea ratio

drop below 40 the values for blood urea increase markedly, when the value of 10 is reached the urea concentrations of the blood show a precipitous rise. These results for partially nephrectomized rats confirm reports on nephritic patients by showing that the value for blood urea does not rise until the renal function is reduced one-half and that there is a marked rise in the values for blood urea as the renal damage increases.

*Blood Pressure*—Page<sup>6</sup> recently presented evidence to show that high blood pressure is not essential for the maintenance of renal function in patients with chronic Bright's disease.

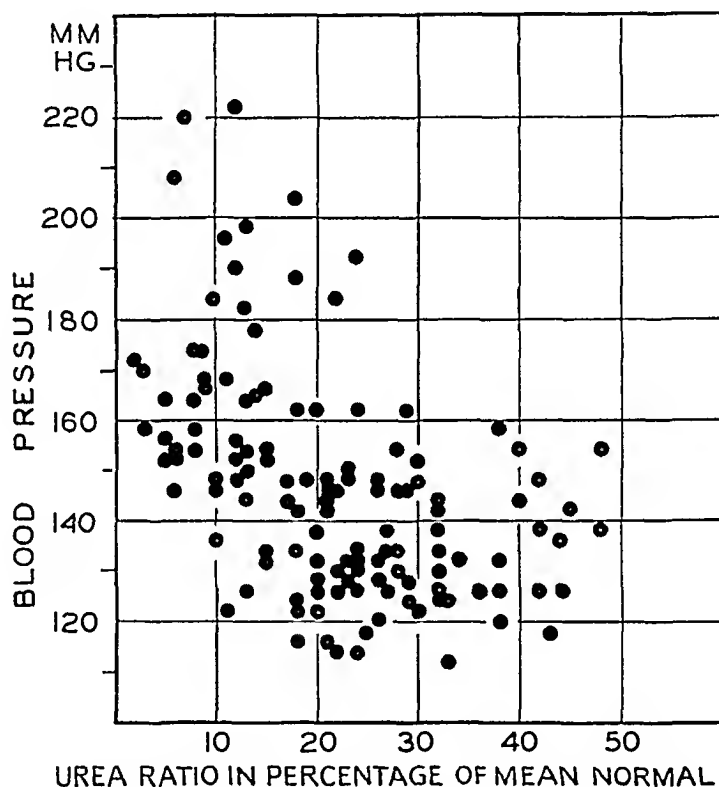


Chart 2—The relation between the Addis ratio (percentage of normal) and the blood pressure

The relation between blood pressure and renal function in partially nephrectomized rats is shown in chart 2. All animals having a ratio below 10 have blood pressures above the normal limits (140 mm), more than half the values being above 160 mm. An appreciable number of animals with a ratio between 10 and 20 have pressures within the normal range, but the majority of them have various degrees of hypertension. The animals with renal function above the percentage urea ratio of 20 show moderate increase in blood pressure in an appreciable number of cases, but most of the values are normal. The variations at any given ratio are large and are not due to dietary differences. Hyperten-

sion is always encountered in cases of renal insufficiency, but the height of the blood pressure cannot be predicted. There appears to be a compensatory effort to overcome mechanical resistance, at first postulated by Traube,<sup>7</sup> in animals that were fed whole meat and that had lowered renal function.

*Urinary Specific Gravity*—Alving and Van Slyke<sup>2</sup> recently published a comprehensive study in which the urea clearance was compared with the specific gravity of urine obtained during concentration tests in persons with nephritis. They concluded that the results of concentration tests are good qualitative indicators of renal function but do not serve to measure the extent of renal damage. It was pointed out that

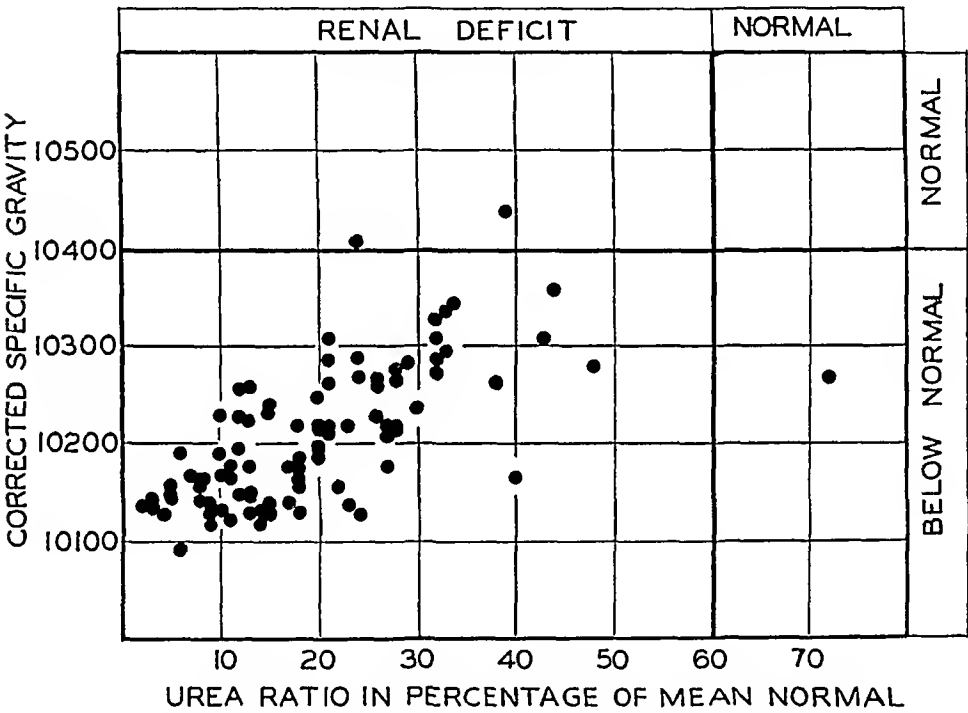


Chart 3—The relation between the Addis ratio (percentage of normal) and the corrected urinary specific gravity

the significance of these two tests is different in that the urea clearance test measures the ability to excrete urea and the concentration test measures the ability of the kidney to concentrate mineral salts.

The corrected specific gravities of urine obtained from partially nephrectomized rats during a concentration test were compared with the urea ratio in percentage of the mean normal value in chart 3. No points fall within the normal range. The few specific gravities above the lower

7 Traube, L. Ueber den Zusammenhang von Herz und Nierenkrankheiten, Berlin, A. Hirschwald, 1856, p. 59.

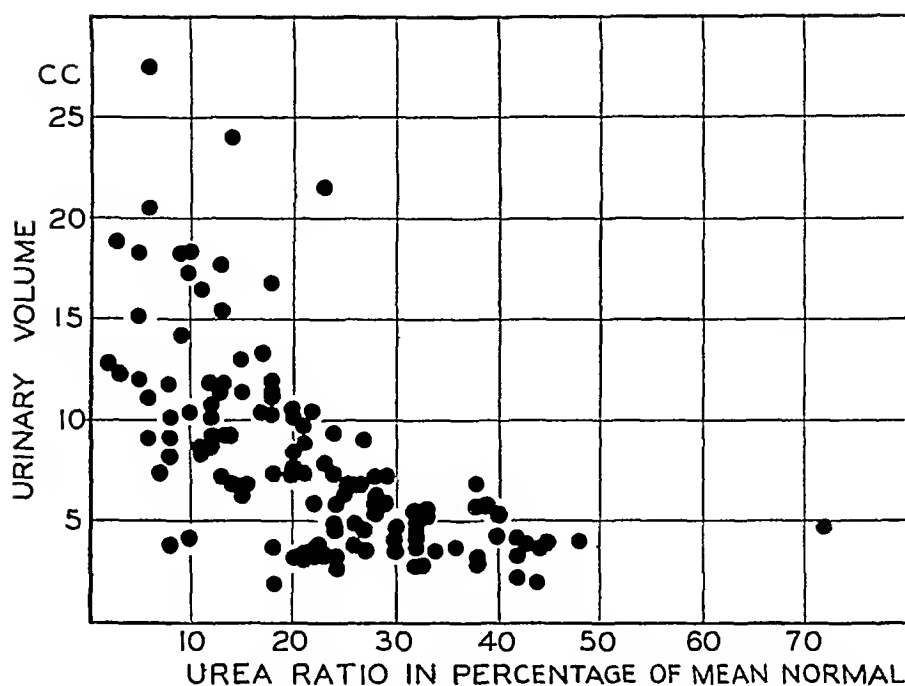


Chart 4—The relation between the Addis ratio (percentage of normal) and the urinary volume

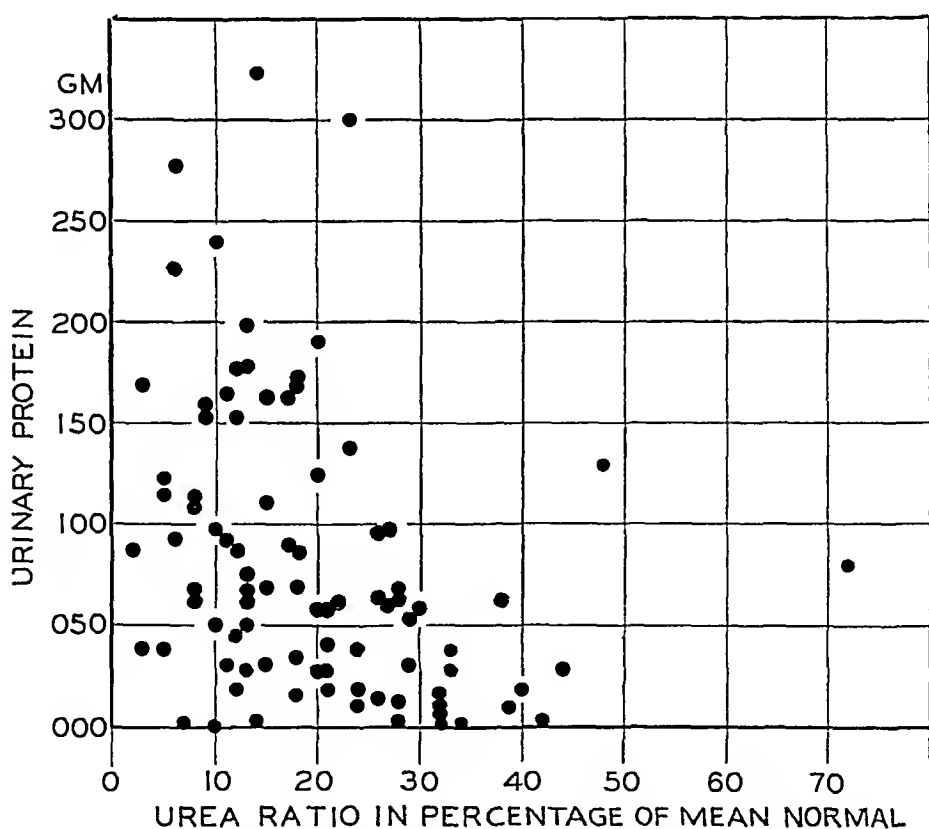


Chart 5—The relation between the Addis ratio (percentage of normal) and the degree of proteinuria



limits of normal (1.04) definitely fall in the range of renal insufficiency. Since there is a good correlation between specific gravity and urea ratio, it may be concluded that the specific gravity is a good indicator of renal function.

It was noted that low specific gravity was maintained for a long period in individual animals but that the urea ratio continued to drop during a similar period. An animal may survive for a comparatively long time with this inability to concentrate, but a drop in the urea ratio was invariably soon followed by death. Furthermore, the urea ratio was a better indicator of hypertension than was the specific gravity of the urine. The evidence in this paper is in accord with the statement "The extent of urine specific gravity fall shows no such uniform relationship to the severity of renal disease as does the urea clearance."<sup>2</sup>

*Urinary Volume*—The diagrammatic representation of volume and urea ratio in percentage of mean normal is presented in chart 4. The highest volumes obtained during the concentration test were between the ratio values of 0 and 20. The volumes decreased as renal function increased. The volumes excreted above the percentage ratio of 30 were fairly constant and within the normal range. The urinary output cannot be predicted during a concentration test, since diet determines the excretion of urine at any given urea ratio, particularly in severe renal insufficiency.

*Proteinuria*—In chart 5 the amount of protein excreted during the concentration test is compared with the percentage urea ratio. It can be seen that there is no relationship between these two factors. Although the highest output of protein was noted in animals with severe renal insufficiency, the marked variations for any given diet eliminate any conclusion concerning this relationship.

#### SUMMARY AND CONCLUSIONS

The blood urea and blood pressure and the specific gravity (after correction was made for albumin), volume and protein content of the urine collected during a concentration test were compared with the urea ratio,  $\frac{\text{urine excreted per hour}}{\text{urea in 100 cc blood}}$ , in partially nephrectomized rats.

The concentration of urea in the blood after the administration of urea is a good measure of the amount of functioning renal tissue. The most marked variation in the amount of urea in the blood was noted in animals with severe renal insufficiency.

Hypertension of various degrees is encountered in all animals with severe renal insufficiency. An estimation of the degree of renal damage cannot serve as a guide for the prediction of blood pressure.

The specific gravity of the urine serves as a good qualitative test for the detection of damaged renal function

The urinary volume was extremely variable and was greatest with marked renal damage. There was good correlation between the extent of renal damage and the amount of urine excreted. The excretion of protein was too variable to show any correlation with renal function.

The results obtained for partially nephrectomized animals are similar to those noted for patients suffering from renal insufficiency.

**S.M.S. MEDICAL COLLEGE,  
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PNEUMONIA DUE TO TYPE I PNEUMOCOCCUS  
ANALYSIS OF DEATHS IN CASES IN WHICH SERUM TREATMENT  
WAS USED

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AND

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It has been proved that specific serum definitely reduces the mortality in pneumonia due to type I pneumococcus. This fact has been amply demonstrated by several careful studies<sup>1</sup> on large series of subjects, which, if taken together, total many thousands of patients treated with serum and a comparable number of controls. However, it is disconcerting that in the very reports which are submitted to prove the value of the treatment it is stated that a not inconsiderable number of patients treated with serum succumb in spite of its use. In the series studied by Park and his associates<sup>1a</sup> from the Bellevue, Harlem and New York hospitals, there was a mortality of 19 per cent in the cases in which serum treatment was used, and in the series reported by Cecil and Plummer<sup>1b</sup> there was a mortality of 20.1 per cent.

From 1929 to 1934 we have had under our care one hundred and eighty-five patients with pneumonia due to the type I pneumococcus that were treated with specific serum, forty-four (23.7 per cent) of

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From the Department of Medicine, New York University College of Medicine, and the Medical Service of the Third (New York University) Medical Division, Bellevue Hospital.

1 (a) Park, W. H., Bullowa, J. G. M., and Rosenbluth, M. B. Treatment of Lobar Pneumonia with Refined Specific Antibacterial Serum, *J. A. M. A.* **91** 1503 (Nov. 17) 1928. (b) Cecil, R. L., and Plummer, N. Pneumococcus Type I Pneumonia, *ibid.* **95** 1547 (Nov. 22) 1930. (c) Cole, Rufus. Serum Treatment in Type I Lobar Pneumonia, *ibid.* **93** 741 (Sept. 7) 1929. (d) Cecil, R. L., and Sutliff, W. D. Treatment of Lobar Pneumonia with Concentrated Antipneumococcus Serum, *ibid.* **91** 2035 (Dec. 29) 1928. (e) Wadsworth, A. B. Review of Recently Published Reports on Serum Treatment of Type I Pneumonia, Together with Report of Four Hundred and Forty-Five Additional Cases, *Am. J. Hyg.* **4** 119 (March) 1924. (f) Sutliff, W. D., and Finland, Maxwell. Type I Pneumococcus Infections with Especial Reference to Specific Serum Treatment, *New England J. Med.* **210** 237 (Feb. 1) 1934. (g) Finland, Maxwell. The Serum Treatment of Lobar Pneumonia, *ibid.* **202** 1244 (June 26) 1930.

the patients died. The purpose of this study was to make a careful inquiry into each of the fatal cases to determine, so far as possible, the factors which contributed to the unfavorable outcome. We believed that a more intensive study of the fatal cases might be fruitful in suggesting improvements in management and that it might supply new evidence for or against the value of serum.

An analysis was made of the following factors, since they seemed the ones most likely to be informative: (1) age, (2) duration of the disease at the time serum treatment was instituted, (3) anoxemia, (4) results of blood culture, (5) amount of serum given, (6) complications and associated diseases, and (7) serum as a cause of death.

#### FACTORS INFLUENCING MORTALITY RATE

*Age*—In table 1 we have shown the age incidence by decades of the patients who recovered and of those who died. It will be noted that whereas no patients in the second decade of life were lost, in 16.6

TABLE 1—*Age Distribution by Decades of Patients Who Recovered and of Those Who Died*

Age	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80
Patients who recovered	0	5	20	35	51	24	5	1
Patients who died	0	0	4	4	11	17	6	2
Total number of patients	0	5	24	39	62	41	11	3
Percentage of mortality	0	0	16.6	10.2	17.7	41.4	54.5	66.6

per cent of those in the third, 10.2 per cent of those in the fourth and 17.7 per cent of those in the fifth the condition terminated fatally. After the age of 50 there was an appreciable rise in the mortality rate, so that among the patients in the sixth decade 41.4 per cent were lost, among those in the seventh 54.5 per cent and among those in the eighth 66.6 per cent. Of the forty-four patients that died, twenty-five were over 50 years of age.

It would appear from these observations that patients over 50 years of age have a severe handicap, based on age alone, in their struggle with this disease.

It is interesting that whereas it is the common impression that infection due to the type I pneumococcus is largely a disease of young people, of our one hundred and eighty-five patients, one hundred and seventeen were over 40 years of age.

*Duration of the Disease at the Time Serum Treatment Was Instituted*—It has been shown by several investigators<sup>2</sup> that in patients who

2 Sutliff, W. D., and Finland, M. Type I Lobar Pneumonia Treated with Concentrated Pneumococcic Antibody (Felton), J. A. M. A. 96:1465 (May 2) 1931.  
Footnote 1 a, b, d, f and g

are given serum within the first three days of their illness, the results are far better than in those who are treated later

In table 2 we have shown the period of the disease when serum was first administered to the patients who recovered and to those who died. We have indicated also the percentage of each group whose treatment was begun in each period. The time of onset was fixed by the occurrence of a chill or of thoracic pain, whenever these symptoms were present. In their absence an approximation of the time of the onset was made by determining the period during which the patient was confined to bed with fever and cough. Analysis shows there was an even age distribution in the various categories.

It will be seen, by comparing the time at which treatment was begun (table 2), that of the patients who recovered 49.6 per cent were treated during the first three days and 91.4 per cent during the first week, and of those who died, only 9 per cent were treated during the first three days and only 56.7 per cent during the first week. Conversely, in the

TABLE 2—*Correlation Between Rate of Mortality and Number of Days After Onset That Serum Treatment Was Instituted*

No. of days after onset that serum therapy was started	1-3	3-7	7-14	14+
141 patients who recovered {Number	70	59	11	1
who recovered {Percentage	49.6	41.8	7.8	0.7
44 patients who died {Number	4	21	14	5
who died {Percentage	9	47.7	31.80	11.3
Percentage of mortality	5.4	26.2	56	83

group that recovered only 8.5 per cent were treated after one week, while in the group that died 42.4 per cent were treated after one week. Only four of the patients who died were treated within three days of the onset. In twenty-one cases a period of from three to seven days elapsed before treatment, and in nineteen cases the period was longer than one week. The delay in treatment was usually due to the patient's late entry into the hospital. In a few cases it was due to difficulties in determining the type of the pneumococcus, either because of absence of sputum, in which case we were forced to await the results of blood culture, or because of an error in the preliminary typing. These difficulties in typing have become infrequent since the introduction of the direct method of Neufeld.

Table 2 shows the correlation between the effectiveness of serum therapy and the stage of the disease at which the treatment was instituted. When therapy was delayed, there was a rapid rise in the rate of mortality. Of the patients treated within the first three days after the onset of the disease, the mortality was 5.4 per cent, of those treated from three to seven days after the onset, the mortality was 26.2 per

cent, of those treated from seven to fourteen days after the onset, the mortality was 56 per cent, and of those treated fourteen days or later after the onset, the mortality was 83 per cent

*Anoxemia*—The relation of anoxemia to fatal outcome was studied in all cases by carefully noting the presence or absence of the clinical signs of anoxemia and in fifteen of the cases also by determining the oxygen saturation of the arterial blood. Some clinical signs, especially cyanosis, tachypnea, tachycardia, nervous irritability, delirium and somnolence, were present in every case. In a small number of cases the anoxemia not only was present but was the outstanding clinical feature. Cyanosis, which in the average case was limited to a faintly blue tinge in the beds of the finger-nails, in the cases of more severe involvement was darker and was readily apparent not only in the beds of the finger-nails but in the mucous membranes and in the skin. A report of one such case follows

CASE 43—J. D., a man 38 years of age, was admitted to the hospital on the third day of illness. The sputum showed the type I pneumococcus. The blood culture was negative. Serum therapy was started early, and 800,000 units was given in all. Cyanosis, noted from the beginning, became gradually more intense. Jaundice was present. The icterus index was 65. Two subsequent blood cultures were negative, and the blood showed a 4 plus reaction for type I agglutinins.

On the sixth day an analysis of the gases in the arterial blood showed the oxygen saturation to be 86 per cent. On the seventh day the oxygen saturation was 85 per cent, and on the eighth day, 82.5 per cent. On the ninth day the patient appeared to be dying. The respiratory rate was 40, and the pulse rate was 130. He was comatose, deeply jaundiced and extremely cyanotic. On the twelfth day the oxygen saturation was 79.7 per cent. He died on the thirteenth day. Post-mortem examination showed the presence of lobar pneumonia, fibrinous pleurisy and bilateral hydrothorax. When a section of the lung was made, pus exuded from the bronchi. Microscopic examination of the kidneys showed acute interstitial nephritis.

This case is of particular interest because it gives a clue to the mechanism causing death in certain cases of pneumonia. As will be pointed out later, in 79 per cent of the fatal cases the condition was associated with bacteremia, and death in these cases was commonly caused by some septic complication. In case 43 several blood cultures were made, but at no time was bacteremia demonstrated. The entire clinical picture was dominated by the signs of lack of oxygen. Not only was there cyanosis, which from day to day became deeper, but an examination of the arterial blood showed a progressive lowering of oxygen saturation from 86.3 per cent on the fifth day after admission to 79.7 per cent on the twelfth day. The explanation suggested by these facts, in addition to the post-mortem observations, was that the profuse purulent secretion in the bronchial tree acted as an effective barrier against the interchange of gas and caused death by asphyxia.

In the following case the patient presented a similar clinical picture of progressive anoxemia with absence of bacteremia

CASE 12—S B, a man 56 years of age, was admitted to the hospital on the fourth day of illness. There was consolidation of the upper lobe of the right lung. On the day of his admission a deep cyanosis was observed. The sputum showed the type I pneumococcus. The blood culture was negative. He was given 250,000 units of type I serum. Two subsequent blood cultures were negative. His course was rapidly downhill, with cyanosis continuing as the outstanding feature. The patient died four days after admission. Postmortem examination showed the presence of lobar pneumonia, acute fibrinous pleuritis, acute purulent bronchitis and tracheitis, atheromatous changes of the aortic valve, aorta and coronary arteries, nephrosclerosis, and congestion of the brain.

This case in its essential features bears a striking resemblance to case 43. At no time was bacteremia demonstrated, even though blood

TABLE 3—*Percentage of Oxygen Saturation in Fifteen Cases*

Case No	Percentage of Oxygen Saturation
1	75-82
2	70.4-87.2
13	90.4
14	82.7
15	81.6-84
16	75.1
17	86.3-91.6
18	83.0
19	76.8
20	91.6
21	85.5
22	76.8-93.5
23	93.2
24	61.4
25	88.7

cultures were made on three occasions. The clinical picture was dominated by signs of profound anoxemia, so that even on the first day in the hospital deep cyanosis was present. The mechanism of this lack of oxygen was apparent at autopsy when it was noted that the trachea and bronchi were the seat of an extensive inflammation and that their lumens were filled with a seropurulent exudate. In this case, as in the previous one, it seems probable that the cause of death was asphyxia.

In several other cases anoxemia appeared to play a considerable part in the picture of the disease, but because there was a concurrent septicemia it was difficult to estimate clearly its significance. The fifteen cases in which the oxygen saturation was determined were proof of how frequently a severe anoxemia was present. The figures are given in table 3. In only one of the fifteen cases was a value (93.2 per cent) approaching the normal level found, and in only three was the figure above 90 per cent. In six cases the oxygen saturation was between 80 and 90 per cent, in five cases between 70 and 80 per cent and in one case between 60 and 70 per cent. These fifteen cases may

be regarded as reasonably representative of the entire group since they were not selected but were taken at random during one period of the study

*Bacteremia*—Blood for culture was taken from all patients soon after admission. No serum was given until this had been done. If the culture was positive, additional cultures were made daily or every second day. If the culture was negative, only one or two additional cultures were made during the period of the administration of the serum, unless there was some specific indication, such as the occurrence of a chill, of a sharp rise in temperature or of a complication. In several cases only one culture was made because the patient died before further study was possible. In twenty-four of the cases in which the blood yielded the organisms on culture the number of colonies per cubic centimeter

TABLE 4—*Distribution of Cases According to Number of Colonies per Cubic Centimeter of Blood*

No. of Colonies per Cc. of Blood	No. of Cases
1-10	3
10-25	4
25-50	2
50-100	3
100-200	2
200-500	3
500-1,000	4
Over 1,000	3

of blood was counted. In one case, through inadvertence, no culture was made.

No other finding was so striking as the frequency and the severity of bacteremia. It was present in thirty-four, or 79 per cent, of the forty-three cases in which blood cultures were made. In thirty-two of the cases the bacteremia was demonstrated in the first culture, that is, in the blood taken before the administration of serum. In many of these cases an overwhelming bacteremia was already present. This condition is best shown in table 4, in which the twenty-four cases in which the number of colonies per cubic centimeter of blood was determined are grouped according to the number of colonies found. The actual colony counts are given in table 9.

In twenty-six cases one or more cultures were made subsequent to the institution of serum therapy. In eleven of these cases the culture was negative although prior to the administration of serum a culture had been positive. In table 5 we have grouped these cases and also have recorded the dose of serum required to sterilize the blood stream. Several cases are especially noteworthy because of the severity of the bacteremia.



In case 19, in which there were over 1,000 colonies per cubic centimeter of blood, the culture became negative after the administration of 360,500 units of serum. In case 36, in which there were over 1,000 colonies per cubic centimeter, the culture became negative after 200,000 units, in case 1 in which there were over 500 colonies, the culture became negative after 200,000 units, in case 6, in which there were over 300 colonies, the culture became negative after 20,000 units, in case 14, in which there were 271 colonies, the culture became negative after 356,000 units, and in case 15, in which there were 107 colonies, the culture became negative after 350,000 units. In several cases, although the bacteremia did not clear up entirely after the administration of serum, there was a decided reduction in the number of colonies.

*Absence of Bacteremia in Fatal Cases*—As we have shown, most patients with pneumonia who die have sepsis, with or without some

TABLE 5—Cases in Which the Blood Culture Was Positive Before and Negative After the Administration of Serum

Case No	No. of Colonies per Cc. of Blood	Dose of Serum After Which Blood Culture Became Negative, Units
19	Over 1,000	360,500
37	Over 1,000	200,000
1	Over 500	200,000
6	Over 300	20,000
14	271	356,000
15	107	350,000
17	66	260,000
2	50	219,500
3	41	400,000
11	16	70,000
9	1	130,000

complication dependent on it. However, there were in our series of fatal cases eight in which, in spite of repeated blood cultures, no bacteremia was demonstrable. A close scrutiny of these cases seemed desirable in order to determine, if possible, the cause of death. Two cases (12 and 14) have already been described, and it was shown that in both death appeared to be caused by an intense anoxemia. In three other cases (10, 28 and 29) the clinical picture presented by the patient was dominated throughout by the signs of lack of oxygen, but since no postmortem examination was made, we cannot offer any certain explanation of the cause of death.

In the three cases reports of which follow neither bacteremia nor severe anoxemia was observed.

CASE 29—F. M., a man 25 years of age, was discharged from the hospital with the diagnosis of acute bronchitis and toxic dermatitis. In seven days he was readmitted, twenty-four hours after the occurrence of a chill. Two days later signs of consolidation were observed over the lower lobe of the left lung. The sputum showed the type I pneumococcus. The blood culture was negative. Tests

of the skin and eyes gave negative results. The patient was given 300,000 units of type I serum. After the treatment there were defervescence and definite general improvement. On the sixth day after the institution of serum therapy there was a sharp rise in temperature to 104 F, and generalized lymphadenopathy, pains in the joints and urticaria were noted. The symptoms of serum sickness persisted for four days, then there was a further rise in temperature, to 106.2 F, and the patient died suddenly. There was no autopsy.

No certain explanation of the events in this case is offered, but the fact that death occurred suddenly while the patient was in the midst of a severe attack of serum sickness makes it seem possible that death was related to the reaction to the serum.

CASE 25—T. G., a man 70 years of age, was admitted to the service for patients with cardiac disease, with a diagnosis of arteriosclerotic heart disease, rapid auricular fibrillation and heart failure. With rest in bed he improved but was still dyspneic and orthopneic. There was only slight loss of weight. The ventricular rate was 134, with a pulse deficit of 22. The fibrillation persisted. Six days after admission the temperature rose to 104 F, and signs of pneumonia of the upper lobe of the left lung were noted. He was then given digitalis, receiving 36 cat units in a period of four days, but it had little effect on the ventricular rate or on the pulse deficit. He was also given 210,000 units of type I antipneumococcus serum. The blood cultures, taken during the febrile period, were negative. The oxygen saturation of the arterial blood on the day before death was 88.4 per cent. He died ten days after admission, which was four days after the development of the pneumonia. There was no autopsy.

We feel that the pneumonia in this case, occurring as an intercurrent infection in the course of cardiac failure, was of less importance than the heart failure in causing the patient's death.

CASE 34—A. P., a white man aged 43, was admitted to the hospital on the fourth day of illness, with consolidation of the lower lobe of the left lung. There were pain and severe tenderness in the left costovertebral angle and in the left side of the abdomen. A difference of opinion arose as to the condition of the heart, one observer reported that there was no disease, while another thought that there was a chronic cardiac lesion involving the mitral and aortic valves. The urine showed a heavy reaction for albumin and clumps of leukocytes. The blood cultures were negative. He was given 500,000 units of serum. Pulmonary edema developed, and he died four days after the onset. There was no autopsy.

The cause of death in this case is uncertain. Heart disease may have been a factor. The possibility of an acute infection of the kidneys was also considered, because of the costovertebral pain, the tenderness and the pus in the urine. In the absence of a postmortem examination, no definite diagnosis could be made.

An analysis of the eight cases in which there was no bacteremia shows that in five there was profound anoxemia resulting from various causes. One patient died during a severe attack of serum sickness, another had congestive heart failure before the onset of the pneumonia and throughout its course. In the eighth case the cause of death was problematic.

*Dosage of Serum*—A question of major importance was whether the dose of serum had been adequate. Dosage is one factor that can be modified should our experience show that this is necessary.

While we have at no time had an inflexible rule as to the amount of serum to be given, the suggested dose was 10,000 units as soon as the disease was determined to be due to the type I pneumococcus, and succeeding doses of 20,000 units at intervals which varied from two to four hours, thus the total dose for the first day was at least 100,000 units. For a patient with a positive blood culture this dose was doubled. If we arbitrarily assume that even so small a dose as 80,000 units of serum might reasonably be regarded as sufficient, we are forced to admit that eleven of our forty-four patients were inadequately treated. We reviewed the eleven cases to determine why the dose of serum was so small, the explanation for each instance is given in table 6. From this table it can be seen that the two most common reasons for an inadequate dose of serum were a delay in typing and sensitiveness to serum.

TABLE 6—*Cases in Which the Patient Received Insufficient Serum and the Explanation for the Inadequate Treatment*

Case No	Name	Dose, Units	Explanation
4	J W	72,000	Error in preliminary typing
5	C F	20,000	Delay in typing
8	N O	60,000	Delay in diagnosis
11	P S	70,000	Sudden death of patient from embolism of popliteal artery
13	C F	22,000	Sudden death of patient one hour after first dose of serum was administered
18	J S	20,000	Delay in typing
23	J D	1,000	Patient died during administration of serum
26	E A	40,000	Delay in typing
38	R M	60,000	Patient's late entry into hospital
42	P T	40,000	Delay in typing, because of absence of sputum
43	A M	1,000	Serum discontinued because of anaphylactoid reaction

*Complications and Associated Diseases*—We have regarded as complications only those conditions that were directly attributable to the pneumococcic infection and the presence of which was proved either at autopsy or by some clinical procedure, such as a spinal tap or thoracentesis. Many other conditions which were found to coexist but which were not caused by the infection have been grouped separately as associated diseases.

The most frequent complications were meningitis (in seven cases), empyema (in six cases) and bacterial endocarditis (in four cases). These and other less frequent complications are listed in table 7. All the complications, except those in the lung itself or in the pleura, appeared to be due to a localization of the organisms from septicemia. Not infrequently the complication was discovered at a time when the blood culture was sterile, but in every case a preceding bacteremia had been demonstrated. In five cases (1, 2, 3, 15, 19) the blood culture had been positive, but was negative following the institution of serum therapy, but not before the infection had localized and formed another focus.

To review The reason for the failure of serum therapy in these cases is shown For instance, in case 1, in which there were over 500 colonies per cubic centimeter of blood, the culture became negative after the administration of 200,000 units of serum However, the uselessness of sterilizing the blood stream became apparent when we observed at postmortem examination that the patient had not only the pneumonia, empyema and purulent arthritis but also bacterial endocarditis with large vegetations on the tricuspid and mitral valves In case 19, in which there were over 1,000 colonies per cubic centimeter of blood, the blood

TABLE 7—*Frequency of Complications*

	No. of Cases
Purulent meningitis	7
Empyema	6
Acute bacterial endocarditis	4
Purulent pericarditis	3
Purulent bursitis	3
Pleural effusion	2
Pulmonary abscess	2
Acute diffuse glomerular nephritis	1
Acute interstitial nephritis	1
Multiple abscesses of kidney	2
Panophthalmitis	1

TABLE 8—*Frequency of Associated Conditions in Fatal Cases*

	No. of Cases
Coronary disease	5
Nephrosclerosis	5
Chronic valvular heart disease	3
Chronic pulmonary tuberculosis	4
Emphysema	2
Cholecystitis	2
Cholelithiasis	1
Syphilis	2
Embolism of popliteal artery	1
Thrombosis of external iliac artery	1
Sclerosis of the aorta	1
Pyelitis	1
Bronchiectasis	1
Chronic leptomeningitis	1

was sterilized, but the infection had already localized on the meninges In case 15, in which there were 107 colonies per cubic centimeter of blood, although the culture became sterile, at autopsy the presence of meningitis and endocarditis was observed In case 3, in which there were 41 colonies per cubic centimeter of blood, the culture became sterile, but the presence of meningitis was noted at autopsy

Cases such as these are not evidence against the value of serum They do, however, bear witness to the importance of instituting serum therapy at the earliest possible moment Once the bacteremia has localized in a vital structure, no amount of serum will be of avail, and an increase in the dose cannot compensate for a delay in administering it

In table 8 the associated diseases are recorded They occurred mainly in the older patients and consisted in large part of cardiovascular con-

TABLE 9—Analysis of Forty-Four Fatal Cases of Pneumonia Due to the Type I *Pneumococcus* in Which the Patient Was Treated with Serum

Case No	Name	Age	Sex	Oxygen Saturation, %	Use of Alcohol*	Duration of Illness to First Dose of Serum, Days	Blood Culture Before Serum	Total Dose of Serum, Units	Blood Culture After Therapy	Complications	Autopsy†
1	H G	41	M	75.82	++++	25	Positive, 500+ colonies	650,000	Negative after 200,000 units	Endocarditis, pericarditis, empyema, arthritis	Lobar pneumonia R.L.L., L.L.L., and R.M.L., empyema, purulent pericarditis, acute endocarditis with vegetations on tricuspid and mitral valves
2	R S	36	M	70.4872	++	8	Positive, 50+ colonies	361,500	Negative after 210,500 units	Empyema, arthritis	Lobar pneumonia of right lung empyema, brown atrophy of heart
3	B H	22	M			5	Positive, 11 colonies	400,000	Negative	Meningitis pericarditis	Purulent (pneumococcus type I) meningitis, hemorrhothorax, fibrinous pleuritis, lobar pneumonia, serous pericarditis on left
4	J W	49	M		+++	6	Negative	72,000	Positive, 60 colonies		Lobar pneumonia L.L.L. and R.U.L. coronary sclerosis, nephrosclerosis
5	C F	57	M		+++	4	Positive, 500+ colonies	20,000	Not taken		Lobar pneumonia L.L.L., chronic mitral and aortic valvular heart disease, pulmonary edema, nephrosclerosis, suppurative pleuritis
6	W S	57	M		++++	8	Positive, 300+ colonies	205,000	Negative after 20,000 units		Lobar pneumonia left as of aortic valve
7	S S	21	M		No	5	Positive, 19 colonies	80,000	Negative after 20,000 units		
8	N O	15	M		No	7	Positive, 500+ colonies	60,000	Positive, 125 colonies	Cholecystitis, cholelithiasis, fibrinopurulent pleuritis	Lobar pneumonia, healed pulmonary tuberculosis, chronic cholecystitis
9	I D	17	M		+++	23	Positive, 1 colony of pneumococci and 16 of hemolytic streptococci	130,000	Negative for pneumococci, positive for hemolytic streptococci	Pulmonary tuberculosis, syphilis	Chronic ulcerative tuberculosis, lobar pneumonia L.L.L., serous pleural effusion, cardiac hypertrophy
10	V G	38	M		++	8	Negative	190,000	Negative	Jaundice	
11	P S	53	M		No	9	Positive, 16 colonies	70,000	Negative	Embolism of popliteal artery	

12	S B	56	M		No	4	Negative	250,000	Negative	None	Emaciation, lobar pneumonia R U L, sclerosis of aortic valve, sclerosis of aorta, nephrosclerosis
13	R S	30	M	90 4	No	11	Positive, 2 colonies	22,000	Not done	Anaphylactoid reaction	
14	W G	63	M	82 7	++	8	Positive, 271 colonies	350,000	Negative	Azotemia	
15	W M	48	M	81 6 84	+++	5	Positive, 107 colonies	350,000	Negative, later positive	Pericarditis, endocarditis, meningitis, pulmonary abscess	Lobar pneumonia left lung, pulmonary abscess, acute endocarditis with vegetations of mitral and aortic valves, acute diffuse glomerular nephritis, focal renal abscesses, purulent meningitis, endocarditis of right auricle
16	F H	53	M	75 1	++++	21	Positive, 500 colonies	85,200	Not done	None	
17	T H	52	M	86 3 91 6	1 +	2	Positive, 66 colonies	280,000	Negative	None	
18	T S	47	M	88 0	No	1	Positive, 1,000 colonies	20 cc	Not done patient died	Meningitis	Lobar pneumonia R I I, spinal fluid cloudy, pure culture of type I pneumococcus
19	C R	45	M	76 8	No	9	Positive, 1,000 colonies	360,500	Negative	Meningitis (proved by tap)	
20	T Y	70	M	91 6	++++	5	Negative	480,000	Positive, 309 colonies	Meningitis (proved by tap)	
21	J C	70	M	85 5 87	++++	18	Positive, 20 colonies	290,000	Positive, 109 colonies — pneumococci, also Friedlander bacilli	None	Lobar pneumonia of right lung, pulmonary tuberculosis, healed fragmentation of heart muscles on left
22	W H	12	M	76 8 93 5	1 + 1 + 1	16	Positive, 200 colonies	290,000	Positive, 1 colonies	None	
23	T D	29	M	92 9	1 + 1 + 1	2	Positive, 1,000 colonies	Only a few cc	Not done	Anaphylactoid reaction	
24	M S	60	M	61 4	1 + 1 + 1	6	Positive, 6 colonies	112,000	Not done	None	
25	T G	70	M	88 4	1 + 1 + 1	3	Negative	210,000	Negative	Heart failure	
26	T A	65	F		1 + 1 + 1	6	Positive	40,000	Negative	Auricular fibrillation	
27	H K	50	M		++	8	Negative	80,000	Not done	None	
28	R S	50	F		++++	8	Negative	110,000	Not done	Cyanosis ++++	
29	T M	25	M		No	12	Negative	300,000	Not done	Serum sickness	
30	U G	53	M		+++++	10	Positive	80,000	Not done, patient died	Acute bacterial endocarditis	Lobar pneumonia R U L and R M L, pleural effusion, acute endocarditis with vegetations on aortic and aortic valves, pulmonary edema
31	W	11	M			4	Positive	720,000	Positive	None	
32	T P	67	M		No	11	Positive	200,000			

TABLE 9—Analysis of Forty-Four Fatal Cases of Pneumonia Due to the Type I *Pneumococcus* in Which the Patient Was Treated with Serum—Continued

Case No	Name	Age	Sex	Oxygen Saturation, %	Use of Alcohol*	Duration of Illness to First Dose of Serum, Days	Blood Culture Before Serum	Total Dose of Serum, Units	Blood Culture After Therapy	Complications	Autopsy†
33	E D	50	M		No	8	Negative	80,000		Syphilis	Lobar pneumonia L U L, L L L, and R L L, coronary sclerosis, thrombus of exterior iliac artery, chronic lept meningitis
34	A P	43	M		+++	1	Negative	500,000		Pyelitis	Lobar pneumonia R L L, empyema (right), pulmonary edema, cardiac hypertrophy and dilatation, coronary sclerosis, emphysema, bronchiectasis
35	G P	62	M		++++	14	Positive	200,000	None	Empyema	
36	H M	51	M		++++	7	Positive, 1,000 colonies	200,000	Negative	None	
37	R M	51	M		++++	6	Positive	60,000	Not taken, patient died		Cholecystitis, lobar pneumonia R L U and R M L
38	A K	56	M		++	7	Positive, 40 colonies	160,000			
39	H S	55	M		++	6	Positive	500,000	Negative		Lobar pneumonia, multiple abscesses R U L and R M L, acute purulent arthritis, acute ophthalmitis, empyema on left, coronary sclerosis on right
40	W L	66	M		+++	4	Positive	400,000	Positive, innumerable colonies	Panophthalmitis, pneumococcal arthritis, pneumococcal meningitis	
41	P T	56	M		+++	7	Not done, no record	40,000, patient died	Not done, no record		Lobar pneumonia R U L, healed bilateral apical tuberculosis, fibrosis of myocardium, renal sclerosis
42	A M	47	M		+++	4	Positive, 51 colonies	1,000	Positive		
43	J D	38	M		++	3	Negative	800,000	Negative	Jaundice	Lobar pneumonia right lung, hydrothorax, acute interstitial nephritis, cardiac hypertrophy, mild coronary sclerosis
44	S P	72	M		No	7	Positive, 10 colonies	1,160,000	Positive, 18 colonies	Meningitis, endocarditis	Lobar pneumonia R L L and L L L, emphysema, acute vegetative and ulcerative endocarditis

\* The number of plus signs indicates the degree to which alcohol had been used +, occasional use, ++, moderate use, ++++, heavy use, +++++, habitual excessive use

† The abbreviations are R L L, the lower lobe of the right lung, L L L, the lower lobe of the left lung, R M L, the middle lobe of the right lung, and L U L the upper lobe of the left lung

ditions, such as coronary disease, nephrosclerosis, chronic valvular heart disease and arteriosclerosis. The higher mortality rate in the advanced age group is probably dependent to some extent on the presence of associated conditions.

*Deaths Due to Serum*—In a study of this kind, the question presents itself as to whether some of the deaths occurred not in spite of serum treatment but because of it. In only three of the cases did this possibility seem worthy of consideration. In case 23 (J. D., aged 29) the blood culture showed over 1,000 colonies per cubic centimeter. Tests of the skin and eyes gave negative results. During the administration of the first dose of serum, the patient became dyspneic and rigid, he blanched and died within a few minutes, in spite of repeated injections of epinephrine hydrochloride.

In case 13 (R. S., aged 30) the blood yielded the organisms on culture. Tests of the skin and eyes gave negative results. He was given intravenously 11 cc. of serum containing 22,000 units. No reaction was noted until one hour after the injection, when he became agitated and cyanotic and gasped for breath. There was bleeding from the gums. He was given epinephrine repeatedly. The condition persisted for one hour and a half, and the patient died.

The third case (29) has already been described. The patient died during serum sickness, the fact that a possible relationship existed between the serum therapy and death was pointed out. In the first two cases the relationship between the serum and the fatality seemed to be reasonably clear. It is worthy of note that the reactions occurred despite the fact that tests of the skin and eyes of the patients gave negative results.

#### SUMMARY

An analysis of forty-four fatal cases of pneumonia due to the type I pneumococcus in which serum treatment was instituted showed that

- 1 The majority of patients were over 50 years of age
- 2 Almost invariably serum treatment had been started late
- 3 Only 9 per cent of the patients who died were treated within the first three days, in contrast to 49.6 per cent of those who recovered
- 4 The mortality among 74 patients whose treatment was started during the first three days after onset was 54 per cent, among 80 patients treated between three and seven days after the onset, 26 per cent, and among 25 patients treated between seven and fourteen days after the onset, 56 per cent
- 5 Some degree of anoxemia was present in every case. In ten, the anoxemia was so severe as to be a dominant feature.



6 In thirty-four, or 79 per cent, of the cases bacteremia was demonstrated

7 In many of the cases in which bacteremia was observed, the blood culture was sterile after the institution of serum therapy, in others the number of colonies was reduced

8 Eleven patients received an inadequate amount of serum, for the various reasons specified

9 Complications were frequent, especially those caused by hematogenous spread, such as meningitis and endocarditis

10 The number of conditions associated with the disease, especially in the older patients, perhaps contributed to the higher mortality rate among them

# EFFECT OF FEEDING OF THYROID OR SALT AND OF THYROIDECTOMY ON FLUID EXCHANGE OF CATS WITH DIABETES INSIPIDUS

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AND

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A marked and permanent increase in the water exchange of the body, which we believe represents true diabetes insipidus, is caused in cats and monkeys by lesions in the hypothalamus which interrupt bilaterally the supra-optico-hypophyseal tracts. The autopsy picture in these animals has shown degeneration of these tracts in the pituitary stalk and a disappearance of the plexus formed by their fibers in the pars nervosa of the hypophysis. Atrophy of the supra-optic nuclei and of the posterior lobe is always associated with degeneration of the supra-optico-hypophyseal tract (Fisher, Ingram and Ranson,<sup>1</sup> Fisher, Ingram, Hare and Ranson,<sup>2</sup> Ingram, Fisher and Ranson<sup>3</sup>)

While the cats with experimental diabetes insipidus were under observation, experiments were conducted to determine the relation of the thyroid gland to the polyuria by removing the gland in three cats and by feeding thyroid to a considerably larger number. The effect on the water exchange of feeding fairly large quantities of sodium chloride was also studied. The results obtained in these experiments are of some interest in relation to the difficult problem of the etiology of diabetes insipidus, and they throw light on the mechanism of the regulation of water metabolism generally.

## METHODS

The mode of production, development and course of diabetes insipidus in a number of the animals used in this investigation have been reported in another article (Fisher, Ingram and Ranson<sup>1</sup>). The operative procedure and the after-care of the additional animals used were the same as those previously described.

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1 Fisher, C, Ingram, W R, and Ranson, S W. Relation of Hypothalamico-hypophyseal System to Diabetes Insipidus, *Arch Neurol & Psychiat* **34** 124 (July) 1935

2 Fisher, C, Ingram, W R, Hare, W K, and Ranson, S W. The Degeneration of the Supra-Optico-Hypophyseal System in Diabetes Insipidus, *Anat Rec* **63** 29, 1935

3 Ingram, W R, Fisher, C, and Ranson, S W. Experimental Diabetes Insipidus in the Monkey, *Arch Int Med* **57** 1067 (June) 1936

The cats were kept on a constant daily diet of 60 Gm of ground beef hearts and 100 cc of milk and were given a measured excess of water each day. The thyroid<sup>4</sup> and sodium chloride were administered by mixing them with the ground beef hearts. The following animals, fifteen in all, were fed varying doses of thyroid for varying periods:

Two cats with marked permanent polyuria (166 and D 16)

Two cats with moderate permanent polyuria (125 and 168)

Two thyroidectomized cats with marked permanent polyuria (91 and D 5)

Two cats with moderate polyuria which had diminished so that the excretion was approximately normal at the time the thyroid was fed (D 6 and D 18)

Two cats which had undergone subtotal removal of the neuro-intermediate lobe of the hypophysis (H 1 and H 2). The anatomic observations on these two animals have been reported in another article (Fisher, Ingram, Hare and Ranson<sup>2</sup>). Neither of these cats showed permanent polyuria following operation.

Five normal cats (T 1, L 1, L 4, L 5 and N 46)

The fourteen cats which were fed salt may be divided into the following groups:

Two cats with marked permanent polyuria (91 and D 32)

One cat with moderate permanent polyuria (125)

Two cats with moderate polyuria which had diminished so that the excretion was approximately normal at the time the salt was fed (D 6 and D 18)

Two cats which had undergone subtotal removal of the neuro-intermediate lobe of the hypophysis (H 1 and H 2)

Seven normal cats (L 1, L 2, L 4, T 1, N 7, N 8 and N 10)

Bilateral thyroidectomy was performed on three animals with marked permanent polyuria: in cat 91 after diabetes insipidus had been present for about five months and in cats D 5 and D 9 two months after the onset of permanent polyuria. The operations were performed under aseptic conditions, and the removed thyroid glands were preserved in solution of formaldehyde, sectioned, and stained with hematoxylin and eosin in order to check the completeness of the removal. These three cats were kept on the same diet after operation as before, and careful records were made of the fluid exchange in order to determine whether the thyroidectomy had any influence on it.

#### RESULTS IN NORMAL CATS

*Effect of Thyroid*—The five normal animals (table 1) showed only slight increases in the water exchange after being fed large doses of thyroid continuously for several weeks. The most marked increase in the output of urine was noted in cat L 1. The successive columns in table 1, from left to right, indicate that this cat was fed 1 Gm of thyroid daily for eight days, 2 Gm daily during the next five days and 3 Gm during the last five days. The output of urine averaged 104 cc during the four days immediately preceding the feeding of thyroid and the intake of 100 cc of milk, no water being drunk. During the period in which thyroid was given the water exchange was slightly lower than normal, but during the eight days following cessation of the administration of thyroid the output of urine and the intake of fluid increased to an average of 130 cc daily, the greatest output of urine being 220 cc and the greatest intake of fluid being 175 cc on the eighth postfeeding day. The average output of urine and the greatest water exchange in the other normal cats during the period following the cessation of the thyroid feeding were less than in the case of cat L 1, even though larger doses were given. However, in both cat T 1 and cat

4 Armour's thyroid was used in this work.

TABLE 1—The Effect of the Feeding of Thyroid on the Water Exchange of Normal Cats and of Cats with Injury to the Supra-Optic-Hypophyseal System

Cat No	Dose		Time, Days		Water Exchange Before Feeding		Time, Days		Water Exchange During Feeding		Time, Days		Water Exchange After Feeding		Time, Days		Peak of Water Exchange		Time When Peak Occurred	
	Gm	Amount	Average	Amount	Average	Amount	Average	Amount	Average	Amount	Average	Amount	Average	Amount	Average	Amount	Average	Amount	Urine	Fluid
Normal cats																				
T1	1	98	100	3	109	100	3	109	100	3	109	100	3	109	100	3	109	100	3	109
	2	98	100	3	109	100	3	109	100	3	109	100	3	109	100	3	109	100	3	109
	3	98	100	3	109	100	3	109	100	3	109	100	3	109	100	3	109	100	3	109
	4	98	100	3	109	100	3	109	100	3	109	100	3	109	100	3	109	100	3	109
L1	1	104	100	4	92	100	4	92	100	4	92	100	4	92	100	4	92	100	4	92
	2	104	100	4	92	100	4	92	100	4	92	100	4	92	100	4	92	100	4	92
	3	104	100	4	92	100	4	92	100	4	92	100	4	92	100	4	92	100	4	92
	4	104	100	4	92	100	4	92	100	4	92	100	4	92	100	4	92	100	4	92
L4	1	82	100	3	75	100	3	75	100	3	75	100	3	75	100	3	75	100	3	75
	2	82	100	3	75	100	3	75	100	3	75	100	3	75	100	3	75	100	3	75
	3	82	100	3	75	100	3	75	100	3	75	100	3	75	100	3	75	100	3	75
	4	82	100	3	75	100	3	75	100	3	75	100	3	75	100	3	75	100	3	75
L5	1	107	100	3	107	100	3	107	100	3	107	100	3	107	100	3	107	100	3	107
	2	107	100	3	107	100	3	107	100	3	107	100	3	107	100	3	107	100	3	107
	3	107	100	3	107	100	3	107	100	3	107	100	3	107	100	3	107	100	3	107
	4	107	100	3	107	100	3	107	100	3	107	100	3	107	100	3	107	100	3	107
N16	1	100	100	3	100	100	3	100	100	3	100	100	3	100	100	3	100	100	3	100
	2	100	100	3	100	100	3	100	100	3	100	100	3	100	100	3	100	100	3	100
	3	100	100	3	100	100	3	100	100	3	100	100	3	100	100	3	100	100	3	100
	4	100	100	3	100	100	3	100	100	3	100	100	3	100	100	3	100	100	3	100
Cats with permanent polyuria																				
D16	1	377	371	7	349	346	7	349	346	7	349	346	7	349	346	7	349	346	7	349
	2	211	235	7	277	328	7	277	328	7	277	328	7	277	328	7	277	328	7	277
	3	211	235	7	277	328	7	277	328	7	277	328	7	277	328	7	277	328	7	277
	4	211	235	7	277	328	7	277	328	7	277	328	7	277	328	7	277	328	7	277
D5	1	210	253	7	198	416	7	198	416	7	198	416	7	198	416	7	198	416	7	198
	2	210	253	7	198	416	7	198	416	7	198	416	7	198	416	7	198	416	7	198
	3	210	253	7	198	416	7	198	416	7	198	416	7	198	416	7	198	416	7	198
	4	210	253	7	198	416	7	198	416	7	198	416	7	198	416	7	198	416	7	198
D18	1	111	100	7	151	131	7	151	131	7	151	131	7	151	131	7	151	131	7	151
	2	111	100	7	151	131	7	151	131	7	151	131	7	151	131	7	151	131	7	151
	3	111	100	7	151	131	7	151	131	7	151	131	7	151	131	7	151	131	7	151
	4	111	100	7	151	131	7	151	131	7	151	131	7	151	131	7	151	131	7	151
Cats in which polyuria disappeared																				
D6	1	121	100	7	110	112	7	110	112	7	110	112	7	110	112	7	110	112	7	110
	2	121	100	7	110	112	7	110	112	7	110	112	7	110	112	7	110	112	7	110
	3	121	100	7	110	112	7	110	112	7	110	112	7	110	112	7	110	112	7	110
	4	121	100	7	110	112	7	110	112	7	110	112	7	110	112	7	110	112	7	110
D18	1	111	100	7	151	131	7	151	131	7	151	131	7	151	131	7	151	131	7	151
	2	111	100	7	151	131	7	151	131	7	151	131	7	151	131	7	151	131	7	151
	3	111	100	7	151	131	7	151	131	7	151	131	7	151	131	7	151	131	7	151
	4	111	100	7	151	131	7	151	131	7	151	131	7	151	131	7	151	131	7	151
Cats with subtotal removal of posterior lobe																				
H1	1	108	100	7	112	117	7	112	117	7	112	117	7	112	117	7	112	117	7	112
	2	108	100	7	112	117	7	112	117	7	112	117	7	112	117	7	112	117	7	112
	3	108	100	7	112	117	7	112	117	7	112	117	7	112	117	7	112	117	7	112
	4	108	100	7	112	117	7	112	117	7	112	117	7	112	117	7	112	117	7	112
H2	1	108	100	7	112	117	7	112	117	7	112	117	7	112	117	7	112	117	7	112
	2	108	100	7	112	117	7	112	117	7	112	117	7	112	117	7	112	117	7	112
	3	108	100	7	112	117	7	112	117	7	112	117	7	112	117	7	112	117	7	112
	4	108	100	7	112	117	7	112	117	7	112	117	7	112	117	7	112	117	7	112

L4 an average intake of water slightly higher than that attained by cat L1 was observed during the period when 4 Gm of thyroid was being fed daily. It should be noted that cats T1, L1, L4 and L5 showed little or no increase in water exchange after the administration of 1 or 2 Gm of thyroid.

*Effect of Salt*—As indicated in table 2 under the heading "Normal Cats," seven animals that had not been operated on were fed 2 or 3 Gm of sodium chloride for one or two days. In all of these cats diuresis was elicited, the most marked being obtained in cat T1. Table 2 shows that in this case 3 Gm of salt was fed for two days, that the average output of urine for the two days preceding the feeding was 90 cc and that the average intake of fluid was 100 cc. The first day that salt was given the output of urine increased to 165 cc and the

TABLE 2—*The Effect of the Feeding of Salt on the Water Exchange of Normal Cats and of Cats with Injury to the Supra-Optico-Hypophyseal System*

Cat No	Dose		Water Exchange Before Feeding			Water Exchange During Feeding				Water Exchange After Feeding		
			Aver Amt of Urine, Cc	Aver Amt of Fluid, Cc	Time Days	1st Day		2d Day		Aver Amt of Urine, Cc	Aver Amt of Fluid, Cc	Time Days
	Gm	Time, Days				Aver Amt of Urine, Cc	Aver Amt of Fluid, Cc	Aver Amt of Urine, Cc	Aver Amt of Fluid, Cc			
Normal Cats												
L1	3	2	70	100	1	145	100	110	160	100	100	3
L2	3	2	115	100	1	160	145	100	115	95	100	3
L4	3	1	95	100	1	195	155	160	165	80	100	3
T1	3	2	90	100	2	165	185	190	190	112	100	3
N7	3	1	67	95	2	155	180			107	100	2
N8	2	1	75	95	2	70	125			100	87	3
N10	3	1	132	95	2	140	150			115	100	3
Cats with Permanent Polyuria												
91	2	1	502	495	2	700	630			445	380	1
125	3	1	180	170	2	310	370			190	193	3
D32	3	2	330	360	2	525	625	515	535	386	385	4
Cats in Which Permanent Polyuria Disappeared												
D6	3	1	125	100	2	250	220			121	115	3
D6	3	2	112	100	2	205	230	185	225	141	108	3
D18	3	1	117	120	2	215	260			151	163	3
D18	3	2	140	137	2	180	255	260	215	150	113	3
Cats with Subtotal Removal of Posterior Lobe												
H1	3	2	105	117	2	230	255	260	260	121	123	3
H2	3	2	77	100	2	130	220	265	225	123	125	3

intake of fluid to 185 cc, while on the second day the output and intake each amounted to 190 cc. The 90 cc of water consumed in this case probably gives the best measure of the intensity of the increase in the fluid exchange, in none of the other normal cats did the consumption of water equal this amount.

#### RESULTS IN CATS WITH PERMANENT POLYURIA

*Effect of Thyroid*—In this group six cats were included, two with marked permanent polyuria (166 and D16), two thyroidectomized cats with marked permanent polyuria (91 and D5) and two with moderate permanent polyuria (125 and 168). These are listed in table 1 under the heading "Cats with Permanent Polyuria." The two cats with permanent polyuria and the two permanently polyuric thyroidectomized cats all showed marked increases in water exchange after the ingestion of 1 Gm of thyroid daily for eight days, an amount which

had little or no effect on normal cats. The peak of the water exchange in cat 91 after the administration of thyroid was more than three times the average water exchange before the feeding, and in cat 166 there was a doubling of the fluid exchange as a result of the feeding of thyroid. The two cats with moderate polyuria also showed greater increases in the output of urine and the intake of fluid after receiving 4 Gm of thyroid daily for five or six days than did the normal cats which received similar doses. In cat 168 the highest water exchange was about four times as great as the average exchange before the feeding of thyroid. It should be noted that in most instances the increases in the fluid exchange are much greater during the week after the cessation of the feeding of thyroid than they are during the actual period of feeding. Also, the peak of polyuria and polydipsia occurs in most cases during the first few days after the feeding is discontinued, after which there is a gradual diminution in the water exchange.

*The Effect of Thyroidectomy*—Histologic examination of the removed glands showed that the thyroidectomy was complete in cats 91, D 5 and D 9. A parathyroid gland was found enclosed in a common capsule of connective tissue with each removed thyroid. The effect of thyroidectomy on the fluid exchange is indicated

TABLE 3—*The Effect of Thyroidectomy and the Subsequent Feeding of Thyroid on the Water Exchange of Cats with Experimental Diabetes Insipidus*

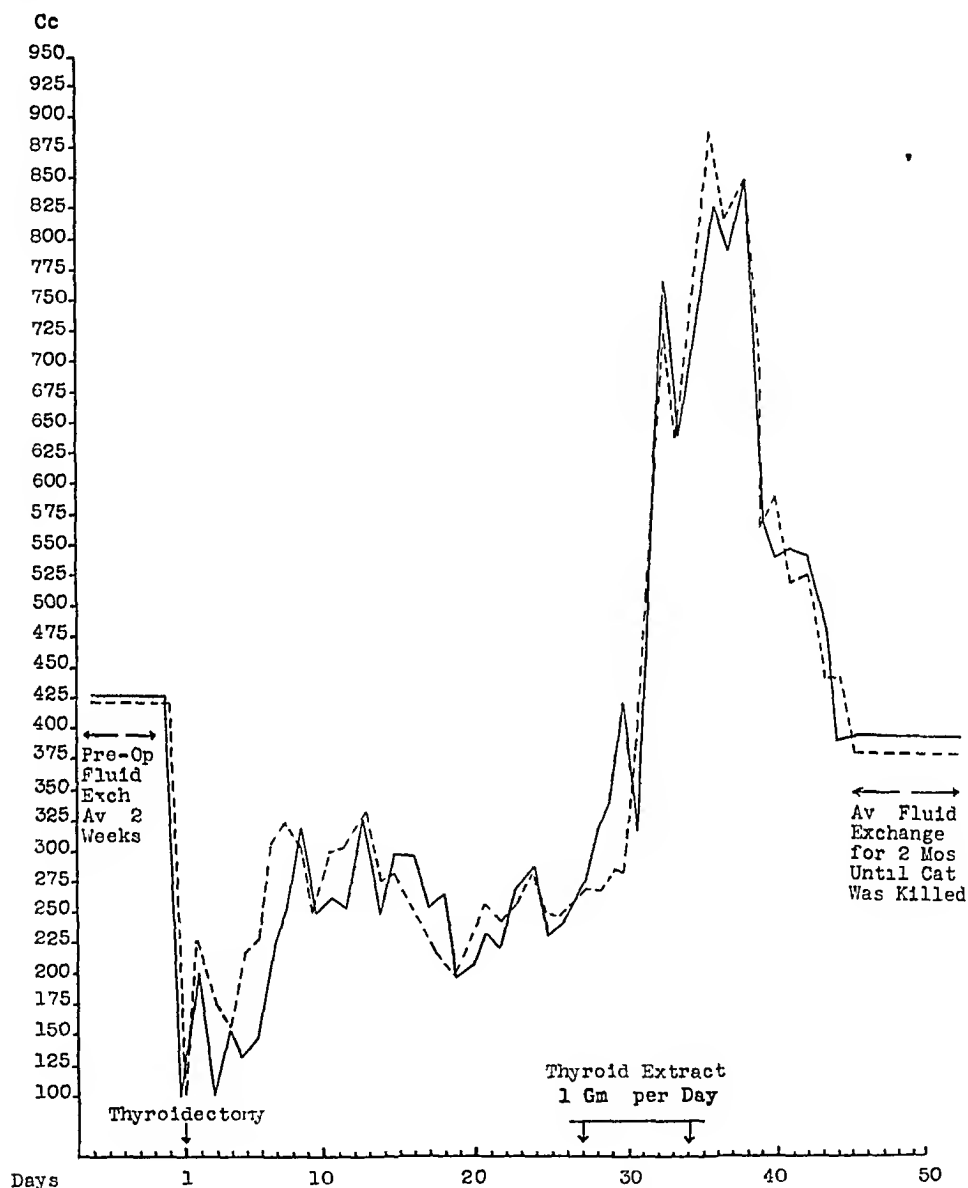
Cat No	Fluid Exchange 2 Weeks Before Feeding		Fluid Exchange Between Thyroidectomy and Thyroid Feeding		Time, Days	Peak Reached During Feeding		Fluid Exchange After Effect of Thyroid Had Passed		Time, Days
	Aver Amt of Urine, Cc	Aver Amt of Fluid, Cc	Aver Amt of Urine, Cc	Aver Amt of Fluid, Cc		Urine, Cc	Fluid, Cc	Aver Amt of Urine, Cc	Aver Amt of Fluid, Cc	
91	341	425	233	252	25	850	905	404	386	60
D5	439	440	331	343	120	600	675	383	373	20
D9	471	499	308	338	12	Became sick and died at end of next 2 wks				

in table 3. In cat 91 there was a reduction of nearly half the fluid exchange during the twenty-five days following thyroidectomy, e g, the average daily output of urine was 431 cc before and 233 cc after operation. At the end of twenty-five days this animal was fed thyroid, as indicated in table 1, and an enormous diuresis resulted. The polyuria and polydipsia gradually decreased after the feeding was stopped, but instead of a return to the level of the fluid exchange prevailing before the feeding of thyroid, a level was maintained during the following two months which more nearly approximated the prethyroidectomy level, e g, an average daily output of urine of 404 cc and an average intake of fluid of 386 cc, as against 431 and 425 cc before thyroidectomy. These results are graphically illustrated in the accompanying chart.

For four months following thyroidectomy cat D 5 showed a reduction in the fluid exchange of about one fourth, as compared with the preoperative level. The output of urine averaged 343 cc, as against 439 cc during the two weeks before operation. During the feeding of thyroid marked diuresis developed (table 1). After the peak of this diuresis had passed the fluid exchange remained higher than before the feeding (as in cat 91) during the period from the seventh to the twenty-seventh day after the administration of thyroid was commenced. The animal was killed twenty-seven days after the feeding of thyroid

was begun. From the seventh to the twenty-seventh day the output of urine averaged 383 cc and the intake of fluid 373 cc. In the last week the output was at as high a level as before thyroidectomy.

Cat D 9 showed a reduction in the fluid exchange of more than one-third after thyroidectomy, the average output of urine falling from 471 cc before operation to 308 cc during the twelve days after operation. At the end of that



Graph showing the effect of thyroidectomy and of the subsequent feeding of thyroid on the water exchange in a cat (cat 91) with diabetes insipidus. The solid line represents the output of urine, the broken line, the intake of fluid.

period the cat became ill and refused food. It died two weeks after the illness set in. During that period the fluid exchange decreased markedly. This animal was not fed thyroid.

*The Effect of Salt*—The three animals (cats D 32, 91 and 125) with permanent diabetes insipidus showed greater absolute increases in the fluid exchange than did the normal controls. These cats are listed in table 2 under the heading "Cats

with Permanent Polyuria." The greatest increase in the output of urine among the normal cats as a result of the feeding of salt was 100 cc, and the greatest increase in the intake of fluid was 90 cc. These increases occurred on the second day of the feeding of salt in the case of cat T 1. On the other hand, cat 91 showed an increase in the output of urine of about 200 cc when fed but 2 Gm of salt for one day and an increase in the intake of water of 135 cc. The experimental feeding of salt was carried out on cat 91 many weeks before thyroidectomy was performed. Similar large increases were observed in the other two animals, cat 125, for example, showing an increase in the intake of water of 200 cc on the day it received 3 Gm of sodium chloride. Cat D 32 showed an increase in the intake of water of 265 cc on the first day it received 3 Gm of salt. After the cessation of the feeding of salt the water exchange quickly declined to normal limits, usually within twenty-four hours, in contrast to the prolonged after-effect of the feeding of thyroid.

#### RESULTS IN CATS IN WHICH MODERATE POLYURIA LATER DISAPPEARED

*Effect of Thyroid*—The two animals (cats D 6 and D 18) in this group are listed in table 1. Cat D 6 showed the usual course of development of polyuria and polydipsia observed in cats with diabetes insipidus. There was an initial transient polyuria which disappeared, followed by the onset of the permanent phase of polyuria ten days after operation. During the three weeks immediately following the onset of the permanent phase the output of urine averaged 188 cc daily and the intake of fluid 195 cc. Shortly thereafter this cat had a severe attack of distemper. For sixteen days little food was consumed, and the fluid exchange decreased markedly. However, the cat continued to drink small amounts of water (from 10 to 60 cc daily) during this period of sickness. After the animal recovered from the distemper and commenced to eat again the polyuria did not return, although the occasional ingestion of small amounts of water gave warning that this was not a normal cat. Two months after recovery from the distemper this cat was fed progressively increasing doses of thyroid (table 1). Although it received less thyroid than three of the normal cats (T 1, L 4 and L 5), a considerably greater diuresis developed, at its peak the output being as high as 250 cc.

A similar disappearance of moderate polyuria took place in cat D 18, this time after recovery from a severe infection of the forelimbs and shoulders. In this case marked transient polyuria developed and gradually disappeared. It was followed by the onset of the permanent phase of the polyuria, on the tenth postoperative day. At the time of onset the severe infection was noted. During the next twelve days the cat consumed little food, but polyuria persisted, the output of urine averaging 205 cc daily and the fluid intake 247 cc. At the end of this period the legs began to heal, and the animal consumed its full diet. At the same time the polyuria began to decrease, and within two weeks the fluid exchange was within normal limits. It remained normal for about two months, after which time the feeding of thyroid was commenced. During this two month period, however, small amounts of water were consumed on a number of occasions. Thyroid was administered at two different periods, separated by an interval of six weeks (cat D 18 is, therefore, listed twice in table 1). Considerable diuresis was elicited on both occasions with doses which had no appreciable effect on normal animals, the water exchange amounting to 225 cc at its peak during the period immediately following the second feeding of thyroid.



*The Effect of Salt*—Cats D 6 and D 18 were fed salt on two different occasions (table 2). Diuresis considerably greater than normal occurred in both these animals after the administration of 3 Gm of sodium chloride. Thus, cat D 6 showed an increase in the output of urine of 125 cc and an increase in the intake of fluid of 130 cc, while cat D 18 showed an increase in output of 120 cc the second day it received 3 Gm of salt. On another occasion cat D 18 increased its intake of fluid by 140 cc the first day it received 3 Gm of salt.

#### RESULTS IN CATS WHICH HAD UNDERGONE SUBTOTAL REMOVAL OF THE NEURO-INTERMEDIATE LOBE

*The Effect of Thyroid*—The anatomic observations on the two cats which had undergone subtotal removal of the neuro-intermediate lobe have been reported in another place (Fisher, Ingram, Hare and Ranson<sup>2</sup>). At that time it was explained that in neither of these cats did polyuria develop spontaneously after the subtotal removal of the posterior lobe. It was believed, however, that the extirpation of most of the neuro-intermediate lobe should be followed by some disturbance in water metabolism, even though the damage to the antidiuretic mechanism was not severe enough to lead to permanent polyuria. It was thought that if these animals were subjected to the strain of diuresis some abnormality would be revealed. The results obtained with the feeding of thyroid in cat H 1 have confirmed this belief (table 1). It is evident that in cat H 1 marked diuresis, which amounted to 375 cc at its peak, was elicited with amounts which had no appreciable effect on normal animals. On the other hand, although cat H 2 appeared to have had as great a deficiency of the neuro-intermediate lobe as had cat H 1, it failed to show diuresis which was significantly greater than that which could be obtained in a normal animal with equivalent doses.

*The Effect of Salt*—As a result of the administration of salt cats H 1 and H 2 showed increases in water exchange which were greater than normal. The increase in cat H 2 was marked, a somewhat surprising result, in view of the fact that abnormal diuresis was not obtained with large doses of thyroid. On the second day that the animal received 3 Gm of salt the output of urine increased by about 190 cc.

#### COMMENT

The results reported show clearly that cats with experimental diabetes insipidus due to injury of the supra-optico-hypophyseal system respond to such diuretics as salt and thyroid with a greater output of urine and a greater intake of fluid than do normal animals. It seems reasonable to suppose that this greater sensitivity toward diuretics is due to a deficiency in the organism of an antidiuretic substance, caused by injury to the supra-optico-hypophyseal system. Presumably this antidiuretic hormone is identical with or closely related to the pressor principle pitressin, which can be extracted from the posterior lobe of the pituitary body. It is therefore of interest that several investigators have reported changes in the content of pressor and antidiuretic substances in the body under varying conditions of water exchange. Thus,

Simon<sup>5</sup> and Simon and Kardos<sup>6</sup> found a decrease in the pressor and oxytocic content of the pituitary glands of rats, guinea-pigs and rabbits which had been subjected to a long period of thirst. This finding was interpreted as indicating an excess secretion of the posterior lobe, in an attempt to prevent the loss of fluid from the body under the condition of thirst, and a consequent diminution of the content in antidiuretic hormone of the secreting gland. Marx<sup>7</sup> reported an increase in the concentration of antidiuretic substance in the blood of fasting dogs and a decrease in the blood taken from a dog at the height of water diuresis. He was able to show that the blood from the fasting dog inhibited the polyuria of the heart-lung-kidney preparation in the same way as did solution of posterior pituitary, while the blood obtained from the dog at the height of diuresis had little or no inhibiting effect. Marx stated that the essential mechanism of water excretion consists of a diminution in the concentration of the antidiuretic substance and a consequent excretion of fluid by the kidney. He reported<sup>8</sup> that the pressor and antidiuretic substance in the blood has many properties in common with the substance obtained from the posterior lobe, and he stated the opinion that if it is not identical with the latter, at least it is closely related to it.

If Marx' view that at the height of diuresis there is a decrease in the concentration of the antidiuretic substance in the blood is accepted, the excessive diuresis obtained in our polyuric animals after the feeding of thyroid and salt can be explained in the following manner. A certain amount of antidiuretic hormone is present in the blood of normal subjects (Marx<sup>8</sup>). During diuresis the resistance which this hormone normally offers to the passage of fluid through the kidneys must be overcome. According to Marx this is accomplished by a decrease in the concentration of the hormone in the blood. In polyuric animals, however, there is already either a greatly reduced content or a complete disappearance of this substance from the blood. Consequently, there is little or no antidiuretic resistance to be overcome, and any tendency toward diuresis finds expression in an exaggerated form.

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5 Simon, A. The Pressor and Oxytocic Content of the Hypophysis of Rats Under Various Conditions, *Am J Physiol* **107** 220, 1934

6 Simon, A., and Kardos, Z. Ueber den Gehalt der Hypophysenhinterlappen normaler und durstender Tiere an blutdruck- und uteruswirksamen Stoffen, *Arch f exper Path u Pharmakol* **176** 238, 1934

7 Marx, H. Zur Theorie der Diurese, *Klin Wchnschr* **9** 2384, 1930

8 Marx, H. Die Bedeutung der Hypophyse für die Erkrankung der Niere, *Klin Wchnschr* **14** 367, 1935

It may be pointed out also that several investigators (Malkin<sup>9</sup> and Dietel and Ditsch<sup>10</sup>) have found thyroid and posterior pituitary to be antagonistic in their effects on water metabolism. From this work it might be expected that a disturbance of the secretory activity of the posterior lobe following injury to the supra-optico-hypophyseal system would lead to an excessive diuretic response after the feeding of thyroid.

The excessive diuresis obtained in the two cats subjected to subtotal removal of the neuro-intermediate lobe (cats H1 and H2) and in the two animals in which moderate polyuria had disappeared (cats D6 and D18) may be explained in the same manner. In the latter two animals the postmortem observations showed that there was a partial destruction of the supra-optico-hypophyseal system, but in each case a considerable number of fibers from the supra-optico-hypophyseal tract escaped interruption. Both cat H 1 and cat H 2 had a remnant of the neuro-intermediate lobe which retained its innervation from the supra-optic nuclei. It seems reasonable to suppose, therefore, that in these four cats the partial destruction of the supra-optico-hypophyseal antidiuretic mechanism was associated with a subnormal content of antidiuretic hormone in the body, but a content still sufficiently great to prevent spontaneous polyuria. An abnormally high water exchange could be observed only under extreme conditions, such as prevail during diuresis due to salt or thyroid.

Several observations in regard to these four animals are somewhat difficult to explain. For example, although cat H2 showed excessive diuresis in response to the administration of sodium chloride, there was a normal response to that of thyroid. The remnant of the gland left in this case was certainly no larger than that found in cat H1. An explanation on the somewhat unsatisfactory basis of individual variation seems to be all that can be offered. A second difficulty is in connection with the disappearance after illness of the moderate polyuria observed in cats D6 and D18. Whether the illness was involved in the disappearance is difficult to decide. Since in both these animals the supra-optico-hypophyseal tracts were partially intact, the polyuria might have disappeared in the absence of illness. It may be noted, however, that the permanent cessation of polyuria, even moderate polyuria, has been a rare occurrence in our experience, although a temporary disappearance has been noted many times during periods of sickness. It has been pointed out (Fisher, Ingram, Hare and Ranson<sup>2</sup>) that the evidence

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9 Malkin, S. J. Ueber den Einfluss einiger Hormone auf den osmotischen Druck der Blutproteine, *Klin. Wchnschr.* **9** 551, 1930.

10 Dietel, F. G., and Ditsch, H. Ueber den Einfluss von Hypophysenhinterlappenextrakt und Thyroxin auf den Wasser-, Natrium- und Chlorgehalt der Gewebe, *Klin. Wchnschr.* **13** 1174, 1934.

favors the view, first promulgated by von Hann,<sup>11</sup> that water metabolism is regulated by a sort of reciprocal action between the anterior and the posterior lobe of the hypophysis and that the diuretic processes in the body are under the control of the anterior lobe. It may well be that the illness in these two cats led to a disturbance of endocrine function which affected the latter processes. At any rate, there is a possibility that disturbances in water metabolism may result not only from the involvement of antidiuretic processes but from diuretic processes as well.

It has been suggested that diabetes insipidus is due to the diuretic activity of the anterior lobe of the pituitary body uncompensated by the antidiuretic action of the neuro-intermediate lobe (Fisher, Ingram, Hare and Ranson<sup>2</sup>). Several recent experiments have indicated possible ways in which the anterior lobe might exert its diuretic influence. Thus, Barnes, Regan and Bueno<sup>12</sup> and Biasotti<sup>13</sup> suggested that the diuresis elicited in dogs after the injection of acid and alkaline extracts of the anterior lobe was due to stimulation of the thyroid gland by the thyrotropic hormone of this lobe of the hypophysis. They found that the basal metabolic rate increased during the injections and that diuresis could not be elicited in animals previously thyroidectomized. Gaebler,<sup>14</sup> however, was able to obtain diuresis in thyroparathyroidectomized dogs after the injection of a commercial preparation of the anterior lobe of the hypophysis said to contain the growth hormone<sup>15</sup>. He stated that the diuretic effect cannot be readily correlated with the stimulation of the thyroid gland or with the increase in the metabolic rate, as has been suggested by Barnes, Regan and Bueno in the case of acid extracts. Later work by Dix, Rogoff and Barnes<sup>16</sup> also suggested that the diuresis is not necessarily associated with the stimulation of the thyroid gland. They found that the diuresis produced in normal animals by the administration of thyroid or extracts of the anterior lobe fails to occur in pancreatectomized dogs, although the metabolic rate is increased. The

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11 von Hann, F. Ueber die Bedeutung der Hypophysenveränderungen bei Diabetes insipidus, Frankfurt Ztschr f Path **21** 337, 1918

12 Barnes, B. O., Regan, J. F., and Bueno, J. G. Is There a Specific Diuretic Hormone in the Anterior Pituitary? Am J Physiol **105** 559, 1933

13 Biasotti, A. Thyroïde et action diurétique de l'extrait antehypophysaire, Compt rend Soc de biol **115** 329, 1934

14 Gaebler, O. H. Effects of Thyroparathyroidectomy and Carbohydrate Intake on the Action of Anterior Pituitary Extracts, Am J Physiol **110** 584, 1935

15 The preparation used was antuitrin G

16 Dix, A. S., Rogoff, J. M., and Barnes, B. O. Diuresis of Hyperthyroidism, Proc Soc Exper Biol & Med **32** 616, 1935

evidence, therefore, does not support the view that the diuretic action of the anterior lobe of the pituitary body is specific and mediated through the thyroid gland

The results which we have reported on the effect of thyroidectomy in polyuric animals can be interpreted as further evidence against the theory that the diuretic action of the anterior lobe of the pituitary body is mediated through the thyroid gland. For if this were true, it might be expected that the removal of the thyroid gland from polyuric animals would bring about a cessation of polyuria. We have shown that such removal leads to a reduction of from a fourth to about a half of the fluid exchange. It is not certain, however, that the thyroidectomy is actually responsible for these decreases, since a number of our animals have shown spontaneous decreases of similar magnitude. The almost complete recovery to the prethyroidectomy level after the feeding of thyroid has been an interesting finding. This level was maintained in the case of cat 91 for two months, and at the end of twenty days cat D5 had attained the prethyroidectomy level, the output of urine on the day before the animal was killed amounting to 515 cc. We can conclude, therefore, that thyroidectomy in these animals causes a moderate decrease in the fluid exchange which can be restored by the feeding of thyroid and which apparently can be maintained at the higher level long after the effects of the thyroid have worn off.

It has been suggested (Fisher, Ingram, Hare and Ranson<sup>2</sup>), in agreement with Richter,<sup>17</sup> that the diuretic activity of the anterior lobe of the pituitary body is general and is brought about by the influence of this gland on growth, metabolism, activity and other phenomena. If the thyroid-stimulating effect is involved, it is only one of what is probably a complex series of processes making for diuresis. For, as Adolph<sup>18</sup> has pointed out "It is apparent that the problem of water balance can never be settled alone. Only in the light of data concerning the regulation and interrelations of every other constituent and force of the cell and of the body can this familiar substance be fully appreciated."

#### SUMMARY

It has been shown that cats with experimental diabetes insipidus due to bilateral interruption of the supra-optico-hypophyseal tracts respond to such diuretics as thyroid and salt with a greater increase in water exchange than do normal cats. Also, cats with partial injury to the supra-optico-hypophyseal system in which permanent polyuria does not develop show similar abnormal increases in water exchange in response

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17 Richter, C. P. Experimental Diabetes Insipidus. Its Relation to the Anterior and Posterior Lobes of the Hypophysis, *Am J Physiol* **110** 439, 1934

18 Adolph, E. F. The Metabolism and Distribution of Water in Body and Tissues, *Physiol Rev* **13** 336, 1933

to these diuretics. The excessive diuresis in these cats has been interpreted as indicating an absence of or decrease in the amount of anti-diuretic substance in the body.

The removal of the thyroid gland from three cats with permanent polyuria resulted in a diminution of the water exchange by from a fourth to a half. The subsequent feeding of thyroid to two of these animals brought on marked diuresis, which was followed by a return not to the prefeeding level but to a level more nearly corresponding to that prevailing before thyroidectomy. This new level persisted long after the effect of the thyroid had worn off. The evidence from these experiments does not support the theory that the diuretic effect of the anterior lobe of the pituitary gland is a specific effect mediated through the thyroid gland.

# EFFECT OF ANOXEMIA ON THE EMPTYING TIME OF THE HUMAN STOMACH

## INFLUENCE OF HIGH ALTITUDES

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WITH THE ASSISTANCE OF DONALD H LOUGH, B S, and CLARK K SLEETH, B S  
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In 1933,<sup>1</sup> attention was called to the fact that the condition of anoxemia is becoming important to an increasingly large number of people. All those who travel by airplane are subjected to a reduced tension of oxygen. There is a still larger group, who suffer from the effects of anoxemia which accompany various diseases. It is well known that anemia as well as certain pulmonary and circulatory disturbances may be complicated by anoxemia.

It was stated in previous papers<sup>2</sup> that hunger contractions as well as digestive peristalses are lessened by the production of anoxemia in the normal dog. In a subsequent paper<sup>1</sup> it was stated that anoxemia distinctly delays the emptying time of the stomach of the normal dog.

In the light of these observations, and especially since gastric symptoms are characteristic of the various disorders mentioned, it was considered well worth while to determine the effect of a lowered tension of oxygen on the emptying time of the normal human stomach.

## METHOD

In order to produce an anoxemic condition, a special, steel respiratory chamber was constructed.<sup>3</sup> The chamber was cylindric and of sufficient size to accommodate comfortably two adults, either in a sitting or in a recumbent position. Windows were provided to serve as a means of communication between the occupants of the chamber and the operator, as well as to illuminate the interior. The chamber could be closed and sealed by an outside operator. The air was exhausted by a large rotary air pump, powered by a suitable electric motor. The capacity of the pump provided adequate ventilation. By means of three inlet valves, air was allowed to enter the chamber in any desired amount.

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From the Department of Physiology, West Virginia University

Aided by a grant from the Committee on Scientific Research of the American Medical Association

1 Van Liere, E J, Crisler, G, and Robinson, D. Effect of Anoxemia on the Emptying Time of the Stomach, *Arch Int Med* **51** 796 (May) 1933

2 Van Liere, E J, and Crisler, G. The Effect of Anoxemia on Hunger Contractions, *Am J Physiol* **93** 267 (May) 1930. Crisler, G, Van Liere, E J, and Booher, W T. The Effect of Anoxemia on the Digestive Movements of the Stomach, *ibid* **102** 629 (Dec) 1932

3 Van Liere, E J. A Respiratory Chamber for Producing Anoxemia in Man, *J Lab & Clin Med* **21** 963 (June) 1936

The principle of producing anoxemia was simple. The air was drawn out faster than it was allowed to enter. The subject was placed in the chamber, the door was closed, and the air pump was started with all the inlet valves open. Then, by slowly closing the valves, the air in the chamber was decompressed to the desired degree and kept at that point. By the use of this method it was possible to secure a low tension oxygen, subject to easy control and yet to provide adequate ventilation for the subject within.

The chamber was connected with a mercury manometer, for the purpose of measuring the degree of decompression of the air. An altimeter was placed within the chamber, in view of the operator, as a further precautionary measure.

Eight normal young adult medical students volunteered for the work. They were given a standard meal,<sup>4</sup> which was prepared in the following manner. Fifteen grams of farina and 1 Gm of salt were added to 350 cc of boiling water and cooked until the total volume was 200 cc. The meal was allowed to cool, and to it was added 50 Gm of barium sulfate, so that the emptying time of the stomach could be determined fluoroscopically. The meal was eaten without difficulty.

The standard meal was always given at 8:30 a. m., the subject having received no other food since the preceding evening. Each man ate the meal several times, and a figure for the normal emptying time of the stomach at atmospheric pressure was established. During the time in which the determination was being made, the subject was requested to relax both physically and mentally as much as possible. After a constant normal figure had been established for each subject, he was given the meal as usual but was placed in the respiratory chamber immediately after he finished eating. The air in the chamber was then decompressed to the desired degree and kept at that point.

An experimental margin of plus or minus fifteen minutes was allowed to compensate for the time needed to remove the subject from the chamber and to examine him under the fluoroscope.

Determinations of the emptying time of the stomach were made at manometric pressures of 560 mm, 515 mm and 460 mm, corresponding with altitudes of approximately 8,000, 10,000 and 14,000 feet, respectively. The respective percentages of oxygen at these altitudes are 15.37, 14.25 and 12.28. Several determinations were made at each pressure. Two students were subjected to an altitude of 18,000 feet, which corresponds to a percentage of oxygen of 10.56.

## RESULTS

The accompanying table and chart show and summarize the results obtained.

*Effect of Anoxemia on the Emptying Time of the Stomach*

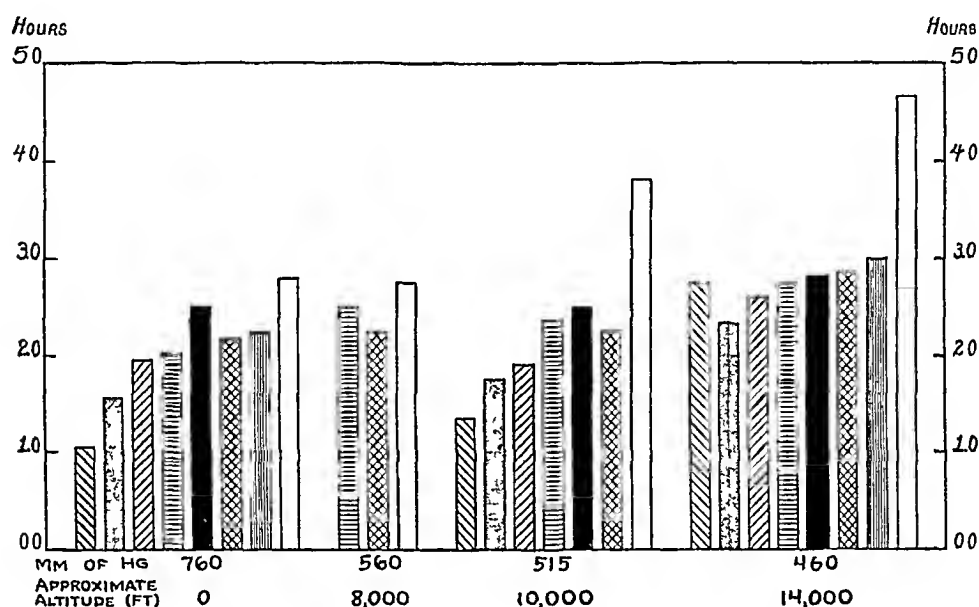
Subject No	Normal, 0 Feet Hours	560 Mm. of Mercury, 8,000 Feet		515 Mm. of Mercury, 10,000 Feet		460 Mm. of Mercury, 14,000 Feet	
		Hours	Percentage of Delay	Hours	Percentage of Delay	Hours	Percentage of Delay
1	1.03			1.33	29.1	2.75	166.9
2	1.55			1.75	12.9	2.33	50.3
3	1.94			1.90	-2.0	2.60	34.0
4	2.02	2.50	21.7	2.37	17.3	2.75	35.6
5	2.50			2.50	0.0	2.83	13.2
6	2.17	2.25	3.6	2.25	3.6	2.87	32.5
7	2.25					3.00	33.3
8	2.80	2.75	-1.8	3.81	36.1	4.67	66.7
Average	2.03		8.5		13.9	2.98	54.1

<sup>4</sup> Personal communication of F. A. Hellebrandt.



It will be seen that there was considerable variation in the normal emptying time of the stomach, the extreme limits being one hour and two and eight-tenths hours, respectively. The average normal time for the eight persons was approximately two hours.

There was definite prolongation of the emptying time of the stomach of two of the three subjects on whom determinations were made at 560 mm of mercury. The emptying time of the stomach of the third man was shortened slightly. Six of the seven subjects on whom determinations were made at 515 mm of mercury showed prolongation, while one was refractory at this pressure. Determinations were made on all eight subjects at 460 mm of mercury, and all showed appreciable prolongation. At this pressure the emptying time of the stomach was



Effect of anoxemia on the individual emptying time of the stomach in eight subjects at various pressures. Each subject is represented by the same type of shading throughout.

in no case prolonged less than 132 per cent of normal, and in one case it was 166.9 per cent of normal.

#### COMMENT

The figures that we obtained for the normal emptying time of the stomach may seem low. It must be remembered, however, that the meal was not large and that it consisted practically entirely of carbohydrate. Since the size and nature of the meal were constant throughout the experiment, we feel that the figures constitute an accurate basis for determining the effects of the experimental conditions. In order to check the accuracy of the normal figures, certain subjects were given the standard meal and placed in the chamber with the door closed and

the motor running but with all the inlet valves open so that the air in the chamber remained at atmospheric pressure. In each case except one, the figure obtained for the normal emptying time of the stomach was identical with that previously established as normal. In the one case the emptying time was slightly shorter than it was outside the chamber. This variation occurred in an active and alert person, the interpretation is that the removal of extraneous influences was responsible for the change.

Great care was exercised in decompressing the air in the chamber as well as in allowing the pressure to return to normal. As a rule it took about five minutes to decompress the air to make it correspond to an altitude of 14,000 feet, and it took the same length of time to allow the air to come back to atmospheric pressure. Unless care was taken in this regard, the men complained of pain in the middle ear. The only other subjective complaint was of an occasional slight headache which would disappear an hour or two after the subject had been removed from the chamber. None of the subjects, however, expressed real apprehension and all willingly returned to the chamber. The psychic factor, therefore, must have been very slight. This is further borne out by the fact that the results of experiments on man described in this paper closely parallel those of the experiments performed on dogs which were reported previously<sup>1</sup>. One must be careful, however, not to draw too close a parallel between the two sets of experiments, as the dogs received considerable protein and fat in their meal, while the meal used for the men consisted practically entirely of carbohydrate. The difference between the food given to the dogs and that given to the men becomes increasingly significant in view of what Hellebrandt and her associates<sup>5</sup> have shown concerning the parallel in function between the mechanism which controls the secretion of the stomach and that which determines its motility.

It is interesting to note that there is considerable individual variation in the response to anoxemia. At a pressure of 560 mm of mercury, corresponding to 15.35 per cent of oxygen and 8,000 feet altitude, two of three men showed a prolongation in gastric evacuation, the other showed a slight acceleration. The acceleration of emptying time was noted also in another person at 515 mm of mercury, or about 10,000 feet altitude. At this pressure the other six men showed a definite prolongation. In one case as much as 36.1 per cent more than normal time was required, this condition was observed in the same person in whom the rate of gastric emptying was accelerated at 560 mm of

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5 Hellebrandt, F. A., Baerstein, H. D., and Hoopes, S. L. Studies in the Influence of Exercise on the Digestive Work of the Stomach, *Am J Physiol* **107** 370 (Feb.) 1934.

mercury We have concluded from our work that the threshold for the average person lies between 6,000 and 8,000 feet

At 460 mm of mercury, which corresponds to an altitude of 14,000 feet and to an oxygen pressure of 12.28 per cent, each subject showed definite prolongation of gastric evacuation Two subjects were highly susceptible, the normal emptying time being prolonged by 66.7 per cent and 166.9 per cent, respectively For the other six men the average prolongation was about 35 per cent

Two men were subjected to a pressure of 380 mm of mercury, which corresponds to an altitude of about 18,000 feet Although the result lay in the same direction, it was less striking than might be anticipated One of the men complained of severe dizziness and intense headache, the latter symptom persisted for from eight to ten hours after he had been removed from the chamber For the most part, however, the pressures used in this work correspond with altitudes common in the Rocky Mountain region of the United States and the high plateaus of the Southwest It is hardly necessary to point out that the native of those regions is undoubtedly well acclimated and in all probability the emptying time of the stomach would be normal

It is to be noted that the results under consideration were obtained on a subject at complete rest There is good reason to believe that even mild exercise at a high altitude would influence the rate of gastric evacuation considerably We are hoping to conduct experiments that will verify this hypothesis

In a recently published article Crisler, Van Liere and Wiles,<sup>6</sup> after working on dogs, pointed out that the delay in gastric emptying time during anoxemia is on a vagospastic pylorospastic basis until a critical threshold is reached, after this point has been passed, further delay is undoubtedly caused by a loss in gastric motility There is every reason to believe that the same factors are operative in man Another mechanism, however, must be mentioned It is generally accepted today that epinephrine is given off during anoxemia Epinephrine could well cause a definite inhibition of motility of the stomach, as has been shown in a recent paper <sup>7</sup>

#### SUMMARY AND CONCLUSIONS

A comparatively simple method of producing anoxemia in man is briefly described

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6 Crisler, G., Van Liere, E. J., and Wiles, I. A. The Mechanism of the Delay in Gastric Emptying Time Caused by Anoxemia, *Am J Digest Dis & Nutrition* **2** 221 (June) 1935

7 Van Liere, E. J., Lough, D. H., and Sleeth, C. K. The Effect of Epinephrine on the Emptying Time of the Human Stomach, *J A M A* **106** 535 (Feb 15) 1936

It was found that under carefully controlled conditions normal adults showed a definite prolongation of the emptying time of the stomach when subjected to anoxemia. The degree of retardation of gastric emptying time varies in the same direction as the degree of anoxemia but in no definite ratio.

The threshold for the average person at rest probably lies between 6,000 and 8,000 feet.

At a pressure of 560 mm of mercury, corresponding with 15.35 per cent oxygen and 8,000 feet altitude, two of three men showed a definite prolongation of gastric emptying time. The third man proved susceptible at a higher degree of anoxemia. One man was refractory at 515 mm of mercury (10,000 feet) but responded at 460 mm of mercury. At the latter pressure, corresponding to an altitude of 14,000 feet and an oxygen pressure of 12.50 per cent, each subject showed a definite prolongation of the emptying time of the stomach—in no case less than 13.2 per cent of the normal time and in one case 166.9 per cent of the normal. Two men were subjected to an altitude of 18,000 feet, the result lay in the same direction.

A brief discussion as to the mechanism involved in the retardation of gastric evacuation appears in the body of the paper.

We feel that since many diseases of man are accompanied by anoxemia and since residence at high altitudes during summer is becoming more and more popular and also since airplane travel is rapidly increasing, these experiments are of distinct interest to clinical medicine.

Besides the two junior authors of this paper the following men served as subjects: K. Gerchow, J. Holt, D. Jones, R. Martin, C. Polan and J. Stratton.

# RED BLOOD CELL VALUES FOR NORMAL MEN AND WOMEN

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AND

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The fundamental importance of accurate standards for hemoglobin content, number of red blood cells and volume of packed cells in the venous blood of normal persons is definitely recognized. Application of these normal values to the study of the various forms of anemia has given the standards clinical as well as academic importance. Possible variations in the normal range of values can be investigated only by comparison of the results of analyses of samples of blood from persons living in a number of widely separated localities which differ in climate and altitude. This comparative study may ultimately make possible the adoption of universal standards or may necessitate the establishment of separate standards for different regions.

Extensive studies of the venous blood of adults have been made in the United States by Haden,<sup>1</sup> in Kansas City, Mo., Cleveland and Detroit, Osgood and Haskins,<sup>2</sup> in Portland, Ore., Wintrobe and Miller,<sup>3</sup> in New Orleans, and Wintrobe,<sup>4</sup> in Baltimore, Foster and Johnson,<sup>5</sup>

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The experimental data in this paper were taken from the thesis submitted by Marjory I. Andresen to the Graduate School of the University of Colorado, in June 1934, in partial fulfillment of the requirements for the degree of Master of Science.

1 Haden, R. L. (a) Clinical Significance of Volume and Hemoglobin Content of the Red Blood Cell, *Arch Int Med* **49** 1032 (June) 1932, (b) Personal communication to the authors.

2 Osgood, E. E. (a) Hemoglobin, Color Index, Saturation Index and Volume Index Standards, *Arch Int Med* **37** 685 (May) 1926. (b) Osgood, E. E., and Haskins, H. D. Relation Between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women, *ibid* **39** 643 (May) 1927.

3 Wintrobe, M. M., and Miller, M. W. Normal Blood Determinations in the South, *Arch Int Med* **43** 96 (Jan) 1929. Wintrobe, M. M. Hemoglobin Standards in Normal Men, *Proc Soc Exper Biol & Med* **26** 848, 1929, Blood of Normal Young Women Residing in a Subtropical Climate, *Arch Int Med* **45** 287 (Feb) 1930.

4 Wintrobe, M. M. Blood of Normal Men and Women, *Bull Johns Hopkins Hosp* **53** 118 (Sept) 1933.

5 Foster, P. C., and Johnson, J. R. Oxygen Capacity and Hemoglobin Content of Normal Blood of Men, *Proc Soc Exper Biol & Med* **28** 929, 1931.

in New Orleans, and Walters,<sup>6</sup> in Lawrence, Kan. None of these cities has an altitude of more than 1,000 feet (304 meters) above sea level.

Wintrobe<sup>7</sup> proposed values for the individual red blood cell, which he termed the corpuscular constants. These values include the volume of the average cell in cubic microns (mean corpuscular volume), the hemoglobin content in micromicrograms (mean corpuscular hemoglobin) and the concentration of the hemoglobin in percentage of unit volume (mean corpuscular hemoglobin concentration). These values are not based on arbitrary standards and are therefore useful in the comparison of the data from different parts of the country. A comparison of such data reveals certain similarities, particularly of the mean corpuscular hemoglobin concentration. It also reveals differences, as of the mean corpuscular volume, which are probably not wholly attributable to technic. Until further studies are reported, the assumption cannot be made that the values for individual corpuscles are everywhere the same.

It is usually stated that with an increase in altitude there is a progressive rise in the number of red blood cells and in the hemoglobin content. The magnitude of this change and the effect on the corpuscular constants have not been thoroughly investigated. Smith, Belt, Arnold and Carrier<sup>8</sup> observed that after the subject had spent four weeks at an elevation of 11,000 feet (3,352 meters) the red blood cells were smaller than those observed when the patient lived at sea level but the concentration of hemoglobin was increased. A period of four weeks may not be sufficient to allow stabilization of these values after a change of altitude. The values obtained by Smith and his co-workers may not be strictly comparable therefore to Hurtado's<sup>9</sup> observations on one hundred and thirty-two Indians of the Peruvian Andes, who had been lifelong residents at an altitude of more than 10,000 feet (3,048 meters). Hurtado found that the individual corpuscles were larger but showed a lower hemoglobin concentration than those of persons living at sea level. He expressed the belief that the adaptation to altitude is not primarily in the increase of red blood cells and hemoglobin but rather in the development of a larger surface area in the individual corpuscles, with a decrease in the hemoglobin concentration. Other factors, such as diet, race and environmental conditions, besides altitude

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6 Walters, O. S. Normal Erythrocyte, Hemoglobin and Packed Cell Volume Standards in Young Men, *J. Lab. & Clin. Med.* **19** 851 (May) 1934.

7 Wintrobe, M. M. The Volume and Hemoglobin Content of the Red Blood Corpuscle, *Am. J. M. Sc.* **177** 513 (April) 1929.

8 Smith, H. P., Belt, A. E., Arnold, H. R., and Carrier, E. B. Blood Volume Changes at High Altitudes, *Am. J. Physiol.* **71** 395 (Jan.) 1925.

9 Hurtado, Alberto. Studies at High Altitude, *Am. J. Physiol.* **100** 487 (May) 1932.

must be considered when Hurtado's observations are compared with those reported in this country

The present study supplies some data on the volume, hemoglobin content and number of red blood cells in the venous blood of average normal adults living at an altitude of about 5,000 feet (1,524 meters). It is also designed to furnish a basis for comparison with a similarly conducted investigation of the blood of children, which is still in progress

### SUBJECTS

The subjects of the investigation were forty white men and forty white women of various nationalities. The group included physicians, medical students, technicians and office workers between 20 and 45 years of age. They were in apparent good health and had been constant residents of this region for at least two years. The work was begun in December and was carried on through the winter, spring and summer months. On fourteen men and eighteen women of the series determinations were repeated at intervals of from seven to fourteen days for a total of six examinations each, and the averages were used in the data for the series

### METHODS

Venous blood and capillary blood are considered equivalent<sup>10</sup> when care is used in obtaining samples from both sources. Since the more accurate methods of analysis require the use of blood in amounts obtainable only by venipuncture, only samples of venous blood were used in the present study

Blood was withdrawn from a vein in the arm, usually between the hours of 9 and 12 in the morning, while the subject was engaged in the usual activities of the day. In securing blood from women no attention was paid to the menstrual cycle, as recent work of Reich and Green<sup>11</sup> has indicated that menstruation produces no significant changes in the values for red blood cells and hemoglobin. Care was taken to avoid undue stasis in the arm from which the sample was collected. The blood was thoroughly mixed in a test tube with 2 mg of dry, iron-free, neutral potassium oxalate for each cubic centimeter of blood. This oxalated specimen was used for all procedures

Red blood cell counts were made on at least two dilutions from each sample of blood. These were repeated until results differing by less than 200,000 cells were obtained, and the average was taken. Hayem's diluting fluid and a Levy-Hausser counting chamber and Thoma pipets certified by the Bureau of Standards were used for all counts

The cell volume was determined for the first fourteen men of the series by the use of Van Allen<sup>12</sup> hematocrit tubes. These were then replaced by the Wintrobe<sup>13</sup> hematocrit tubes, which were found to be more accurate. Samples were centrifuged at 3,000 revolutions per minute in an international centrifuge, type S B,

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10 Osgood, E. E., and Haskins, H. D. *Laboratory Diagnosis*, Philadelphia, P. Blakiston's Son & Co., 1931, p. 345

11 Reich, C., and Green, D. *Red Cell Regeneration during the Menstrual Cycle*, *Arch Int Med* **49** 534 (March) 1932

12 Van Allen, C. M. *An Hematocrit Method*, *J Lab & Clin Med* **10** 1027 (Sept) 1925

13 Wintrobe, M. M. *A Simple and Accurate Hematocrit*, *J Lab & Clin Med* **15** 287 (Dec) 1929

for thirty minutes, a reading of the height of the column of red cells was taken, and centrifugation was continued for five minute periods until there was no further change in volume. The amount of shrinkage due to the potassium oxalate was found by dividing the samples of blood from thirty subjects between tubes containing potassium oxalate and tubes containing heparin. Hematocrit determinations were made simultaneously on the two portions. The average shrinkage from the potassium oxalate was found to be 6.4 per cent, and this correction was made on all the oxalated specimens. On ten of the thirty samples hirudin was also used as an anticoagulant. Six of the ten samples treated with hirudin gave readings identical with those of the heparinized blood, and the maximum difference in any of the other four samples was 0.4 per cent.

Three methods for the determination of hemoglobin were followed as a routine. The Van Slyke-Neill<sup>14</sup> manometric method of gas analysis was used as the standard research procedure to determine the oxygen-carrying capacity of the hemoglobin. From the oxygen capacity in cubic centimeters the hemoglobin content was calculated on the assumption that 1 Gm of hemoglobin combines with 1.34 cc of oxygen. This factor, though it is in general use for the standardization of clinical instruments by the oxygen capacity method, is based on Hufner's<sup>15</sup> analysis of ox blood, and its applicability to human blood has been questioned<sup>16</sup>. It was used in the present study to afford comparison with other data, which are reported in grams.

The determination of hemoglobin from the iron content of the whole blood is often mentioned as a method approaching the Van Slyke technic in research accuracy. The procedure followed consisted of a modification of the original method of Wong<sup>17</sup>. One cubic centimeter of whole blood was diluted with 4 cc of distilled water, and 1 cc of the diluted blood was digested with concentrated sulfuric acid and potassium chlorate. After digestion was complete, the material was diluted to about 10 cc with distilled water, and a drop of saturated potassium persulfate was added to prevent reduction of the iron. The color was developed by the addition of 5 cc of a three times normal solution of potassium sulfocyanate and was immediately extracted by shaking with exactly 25 cc of a mixture of 2 parts of ethyl ether and 5 parts of amyl alcohol. The use of this extraction mixture was taken from the method of Stokes and Cain as described by Reich and Tiedemann<sup>18</sup>. Comparison was made colorimetrically with a standard iron solution digested and treated in exactly the same manner as the unknown. The oxygen capacity of the blood was figured from the iron content on the basis<sup>19</sup> that one milligram atom, or 55.9 mg, of iron binds one milligram molecule, or 22.4 cc, of oxygen measured at 0°C and at a pressure of 760 mm of mercury.

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14 Van Slyke, D. D., and Neill, J. M. The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J Biol Chem* **61** 523 (Sept.) 1924.

15 Hufner, G. Neue Versuche zur Bestimmung der Sauerstoffcapacitat des Blutfarbstoffs, *Arch f Physiol*, 1894, p. 130.

16 Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 524.

17 Wong, S. Y. Colorimetric Determination of Iron and Hemoglobin in Blood, *J Biol Chem* **55** 421 (March) 1923.

18 Reich, C., and Tiedemann, V. G. A Study of Iron Volume Index of the Blood and Its Significance in the Treatment of Anemia, *Am J M Sc* **184** 637 (Nov.) 1932.

19 Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 672.



The Osgood-Haskins<sup>20</sup> method of hemoglobin estimation after conversion to acid hematin was selected as one of the more accurate clinical procedures. The hemoglobin content in grams was calculated from the special table provided with the standard.<sup>21</sup>

Certified glassware was used in the determination of hemoglobin by the iron and the acid hematin method. The chamber of the Van Slyke apparatus and the hematocrit tubes were carefully recalibrated. Colorimetric work was done in a

TABLE 1—*Values for Venous Blood of Normal Men*

	Hemoglobin, Grams in 100 Cc of Blood			Volume of Packed Cells, Cc per 100 Cc of Blood	Red Blood Cells, Millions per Cu Mm	Mean Corpus- cular Hemo- globin	Mean Corpus- cular Volume	Mean Cor- puscular Hemo- globin Concen- tration
	Oxygen Capacity Method	Iron Method	Acid Hematin Method					
1*	18.3	18.3	18.6	53.6	5.38	34.0	99.6	34.1
2*	18.0	18.0	18.3	50.6	5.76	31.2	87.8	35.5
3	17.9	17.9	17.5	51.4	5.99	29.8	85.8	34.8
4	17.7	17.6	17.5	48.1	5.49	32.2	87.6	36.8
5	17.5	17.2	17.3	50.6	5.78	30.2	87.5	34.5
6	17.4	17.6	17.9	51.2†	5.33	32.6	96.0	33.9
7	17.3	17.3	17.3	48.0	5.45	31.7	88.0	36.0
8*	17.2	17.1	17.2	49.7	5.70	30.1	87.1	34.6
9	17.2	17.2	17.3	51.7	5.32	32.3	97.1	33.2
10	17.1	16.5	16.1	49.8	5.53	30.9	90.0	34.3
11*	17.1	17.0	16.8	47.7	5.28	32.3	90.3	35.8
12*	17.0	16.8	17.5	48.5	5.41	31.4	89.6	35.0
13*	16.9	16.5	17.6	47.6	5.69	29.7	83.6	35.5
14	16.8	16.8	16.4	48.6	5.65	29.7	86.0	34.5
15*	16.8	16.5	16.9	47.4	5.02	33.4	94.2	35.4
16*	16.8	16.5	17.2	49.0	6.07	27.6	80.7	34.2
17	16.8	16.3	16.6	49.0†	5.49	30.6	89.2	34.2
18*	16.8	16.4	16.9	51.7	5.67	29.6	91.1	32.4
19	16.7		16.7	48.4	5.22	31.9	92.7	34.5
20	16.7	16.6		48.0	5.44	30.7	88.2	34.7
21*	16.6	16.5	17.4	46.6	5.34	31.0	87.2	35.6
22	16.4	16.6	18.1	49.2†	5.28	31.0	93.1	33.3
23	16.4	15.9	16.0	49.0†	5.57	29.4	87.9	33.4
24	16.3	16.0	17.2	50.1	5.34	30.5	93.8	32.5
25	16.3	16.6		49.0	5.38	30.3	91.0	33.2
26	16.2	16.2	17.2	47.2	5.50	29.4	85.8	34.3
27	16.2	15.9	18.0	48.2†	5.26	30.8	91.6	33.6
28*	16.2	15.8	16.8	47.7	5.52	29.3	86.4	33.9
29*	16.1	16.3	16.5	48.9	5.33	30.2	91.7	32.9
30*	16.0	15.8	17.0	47.0	5.40	29.6	87.0	34.0
31	15.9	15.7	16.4	49.0	5.47	29.0	89.5	32.4
32	15.9	15.2	16.6	45.7	5.43	29.2	84.1	34.7
33*	15.8	15.2	16.1	44.9	5.19	30.4	86.5	35.1
34	15.6	15.5	16.4	47.5	5.33	29.2	89.1	32.8
35	15.5	15.8	14.5	46.2	5.08	30.5	90.9	33.5
36	15.5	15.1	16.8	48.6	5.68	27.2	85.5	31.8
37	15.4	15.9	14.9	44.0	4.99	30.8	88.1	35.0
38	15.3	15.8	15.4	46.6	5.23	29.2	89.1	32.8
39	15.2	15.2	15.3	43.8	5.02	30.2	87.2	34.7
40	15.0			44.3	4.83	31.0	91.7	33.8
Mean	16.54	16.51	16.87	48.35	5.42	30.5	89.2	34.2

\* Average of six determinations

† Heparin used as an anticoagulant

dark room, the same Bausch and Lomb Duboscq colorimeter being used for all readings, with a Bausch and Lomb colorimeter illuminator as the constant source of light.

#### COMMENT

Results obtained from 240 determinations on the forty men and forty women who comprise the present series are listed in tables 1 and 2.

20 Osgood, E. E., and Haskins, H. D. A New Permanent Standard for Estimation of Hemoglobin by Acid Hematin Method, *J. Biol. Chem.* **57**: 107 (Aug.) 1923.

21 The standard and table were furnished by Dr. E. E. Osgood.

From thirty-six men and thirty-nine women sufficient blood was obtained for determinations of hemoglobin by all three methods. The mean values in grams for these members of the series are given in table 3.

The general averages for the values obtained by the three methods are in close agreement. The values obtained by the Osgood-Haskins

TABLE 2—*Values for Venous Blood of Normal Women*

	Hemoglobin, Grams in 100 Cc of Blood			Volume of Packed Cells, Cc per 100 Cc of Blood	Red Blood Cells, Millions per Cu Mm	Mean Corpus- cular Hemo- globin	Mean Corpus- cular Volume	Mean Cor- puscular Hemo- globin Concen- tration
	Oxygen Capacity Method	Iron Method	Acid Hematin Method					
1*	15.8	15.7	15.8	45.9	4.75	33.2	96.6	34.4
2	15.6	15.0	15.7	44.0	4.71	33.1	93.4	35.4
3*	15.4	15.5	14.9	45.0	5.00	30.8	90.0	34.2
4*	15.2	15.3	15.3	44.9	4.66	32.6	96.3	33.8
5*	15.2	15.2	14.7	42.7	4.48	33.9	97.3	35.5
6*	15.3	15.5	15.0	44.2	4.58	33.4	96.5	34.6
7*	14.9	15.0	14.3	44.2	4.51	33.0	98.0	33.7
8	15.0	15.5	14.8	44.9	4.61	32.5	97.3	33.4
9	14.9	15.6	15.4	45.5	4.73	31.5	96.1	32.7
10	14.9	14.1	14.0	44.5	4.78	31.1	93.0	33.4
11	14.8	14.6	14.9	46.1	4.84	30.5	95.2	32.1
12	14.7	15.0	14.6	45.3	4.79	30.6	94.5	32.4
13*	14.9	15.0	14.4	43.6	4.57	32.6	95.4	34.1
14*	14.8	14.9	14.1	44.1	4.61	32.1	95.6	33.5
15*	14.8	14.6	14.6	43.4	4.48	33.0	96.8	34.1
16	14.7	14.7	15.3	44.0†	4.58	32.0	96.0	33.4
17	14.7	15.1	15.3	43.7†	4.94	29.7	88.4	33.6
18*	14.7	14.6	14.1	42.6	4.55	32.3	93.6	34.5
19	14.5	14.4	14.3	43.6	4.63	31.3	94.1	33.2
20	14.5	14.0	14.4	42.7†	4.71	30.7	90.6	33.9
21	14.4	14.0	14.7	44.0†	4.78	30.1	92.0	32.7
22*	14.5	14.5	14.2	43.3	4.59	31.5	94.3	33.4
23	14.4	15.3	13.9	42.4	4.82	29.8	87.9	33.9
24	14.4	15.0	14.2	42.6	4.50	32.0	94.6	33.8
25*	14.4	14.5	13.9	42.6	4.53	31.8	94.0	33.8
26*	14.3	14.5	14.1	41.5	4.47	31.9	92.8	34.4
27*	14.4	14.3	14.1	41.7	4.48	32.1	93.0	34.5
28	14.3	15.0	15.4	46.0	4.62	30.9	99.5	31.0
29	14.3	14.1	13.0	44.2†	4.66	30.6	94.8	32.3
30	14.1	14.1	13.6	43.4	4.54	31.0	95.5	32.4
31	14.1	14.0	13.6	42.9	4.62	30.5	92.8	32.8
32*	14.1	14.0	13.5	41.5	4.55	30.9	91.2	33.9
33	14.0	14.3	13.6	41.3	4.41	31.7	93.6	33.9
34*	14.0	14.3	14.1	42.4	4.65	30.1	91.1	33.0
35	13.9	13.7	14.0	43.9†	4.76	29.2	92.2	31.6
36*	13.6	13.6	13.7	39.9	4.46	30.4	89.4	34.0
37*	13.5	13.5	13.4	41.1	4.45	30.3	92.3	32.8
38	12.9	12.7	13.2	41.1	4.52	28.5	90.9	31.3
39	12.7	12.4	12.7	37.1	4.67	27.1	79.4	34.2
40	12.7	13.1	13.5	41.0†	4.63	27.4	88.5	30.9
Mean	14.45	14.51	14.33	43.22	4.63	31.2	93.3	33.4

\* Average of six determinations.

† Heparin used as an anticoagulant.

acid hematin method checked almost as closely with those from the Van Slyke determinations of oxygen capacity as did those obtained by the iron method.

The frequency distribution of the hemoglobin content in grams as determined by the Van Slyke-Neill oxygen capacity method, of the number of red blood cells and of the volume of packed cells is given in chart 1. Values for corpuscular constants calculated from these figures are graphically shown in chart 2.

Comparison of the mean values with those previously reported by other workers is shown in table 4. All volumes of packed cells are corrected to the volume of heparinized blood.

TABLE 3—*Mean Values for Hemoglobin in Grams per Hundred Cubic Centimeters of Blood*

Men	Method	Mean*	Standard Deviation*	Coefficient of Variation,* Percentage
36	Oxygen capacity	16.58 $\pm$ 0.092	0.82 $\pm$ 0.065	4.9
36	Iron content	16.51 $\pm$ 0.095	0.84 $\pm$ 0.067	5.1
36	Acid hematin	16.87 $\pm$ 0.101	0.93 $\pm$ 0.072	5.5
Women				
39	Oxygen capacity	14.45 $\pm$ 0.074	0.69 $\pm$ 0.052	4.7
39	Iron content	14.51 $\pm$ 0.086	0.80 $\pm$ 0.061	5.5
39	Acid hematin	14.33 $\pm$ 0.073	0.68 $\pm$ 0.052	4.7

\* Computation of statistical data in frequency groups is used in this study (Dunn, H. L. Application of Statistical Methods in Physiology, *Physiol. Rev.* 9: 341 [April] 1929).

TABLE 4—*Values for Venous Blood Reported in the United States*

Authority and Location	Number in Series	Hemoglobin, Gm per 100 Cc of Blood	Volume of Packed Cells in 100 Cc of Blood	Red Blood Cells in Millions per Cu. Mm.	Mean Corpuscular Hemoglobin, Micrograms	Mean Corpuscular Volume, Cubic Microns	Mean Corpuscular Hemoglobin Concentration, Percentage
Osgood, Haskins and Trotman (J. Lab. & Clin. Med. 17: 859 [June] 1932), Portland, Ore.	196 men	15.80	46.35	5.4	29.2	85.8	34.0
	100 women	13.70	42.43	4.8	28.5	83.3	32.2
Wintrobe and Miller, <sup>3</sup> New Orleans	100 men	17.0	49.6	5.85	29.0	84.7	34.2
	50 women	13.76	41.5	4.93	28.0	84.1	33.1
Haden, <sup>1</sup> Kansas City, Mo., Detroit and Cleveland	70 men	15.34	45.5	4.95	31.0	92.0	33.7
	30 women	13.37	39.8	4.38	30.5	91.0	33.5
Foster and Johnson, <sup>5</sup> New Orleans	40 men	15.74	46.7	5.26	29.9	88.7	33.6
Walters, <sup>6</sup> Lawrence, Kan.	100 men	15.12	46.5	4.84	31.4	96.5	32.4
Wintrobe, <sup>4</sup> Baltimore	86 men	16.00	47.0	5.48	29.1	85.7	34.0
	101 women	14.10	42.0	4.82	29.2	87.1	33.5
Mugrage and Andresen, Denver	40 men	16.54	48.35	5.42	30.5	89.2	34.2
	40 women	14.45	43.22	4.63	31.2	93.3	33.4

Wintrobe,<sup>4</sup> from analysis of the data obtained from a number of accurate hematologic determinations in different parts of the United States and Europe, stated that there is no significant geographic variation in values for normal blood. He obtained a general average from these values and also calculated a normal range. The limits of normal

variation which he established for the mean corpuscular hemoglobin volume and hemoglobin concentration were based on his recently reported study of <sup>22</sup> eighty-six men and one hundred and one women. Wintrobe's figures are compared in table 5 with those obtained in the present study.

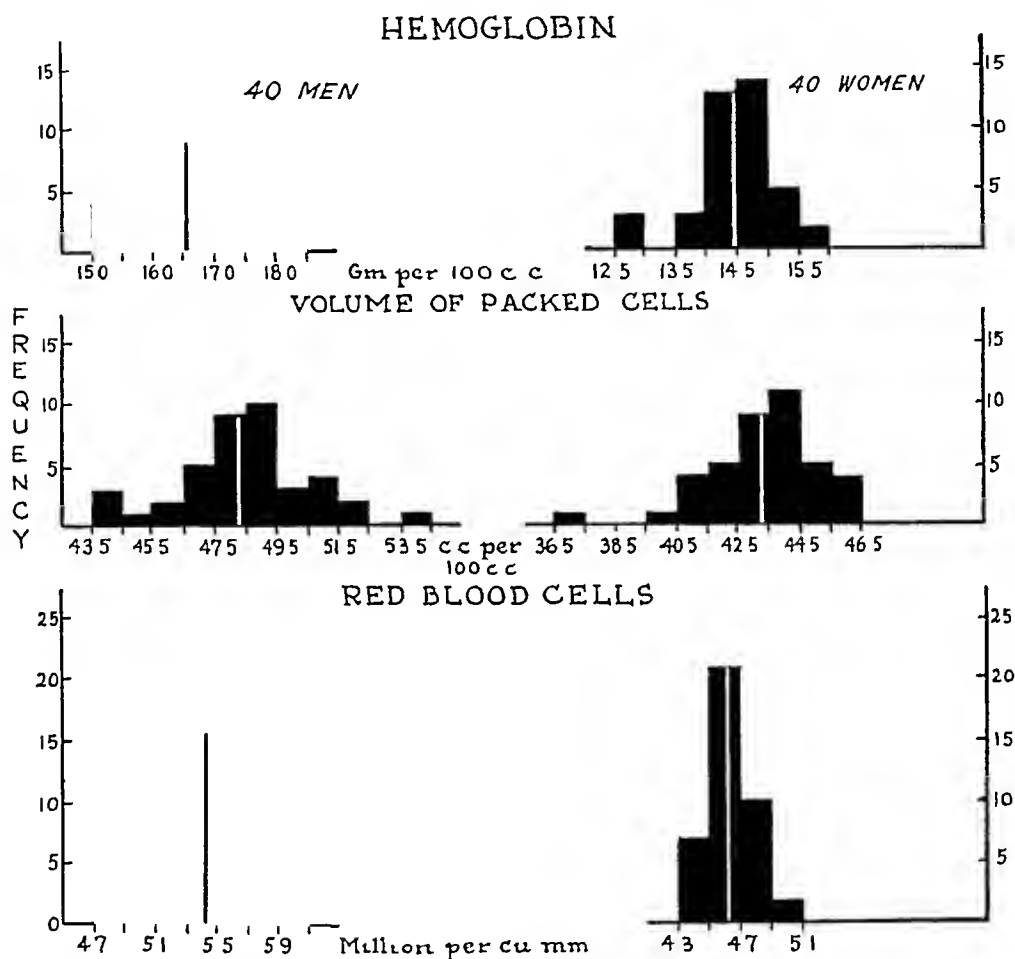


Chart 1—Hemoglobin content, number of red blood cells and volume of packed cells in the venous blood of forty normal men (left) and of forty normal women (right). The white line indicates the arithmetic mean.

The mean hemoglobin content of the blood of the forty men was  $16.54 \pm 0.085$  Gm per hundred cubic centimeters, the standard deviation was  $0.79 \pm 0.06$ , and the coefficient of variation was 4.8 per cent. The mean hemoglobin content of the blood of the women was  $14.45 \pm 0.07$ , the standard deviation was  $0.66 \pm 0.05$ , and the coefficient of variation was 4.6 per cent.

The mean volume of packed cells for the blood of the forty men was  $48.35 \pm 0.231$ , the standard deviation was  $2.16 \pm 0.164$ , and the coefficient of variation was 4.4 per cent. For the blood of the forty women the mean volume of the packed cells was  $43.22 \pm 0.192$ , the standard deviation was  $1.8 \pm 0.136$ , and the coefficient of variation was 4.2 per cent.

The mean red blood cell count for the men was  $5,420,000 \pm 28,000$ , the standard deviation was  $0.26 \pm 0.02$ , and the coefficient of variation was 4.8 per cent. For the women the red cell count was  $4,630,000 \pm 16,000$ , the standard deviation was  $0.15 \pm 0.012$ , and the coefficient of variation was 3.3 per cent.

Tables 4 and 5 both show that values for hemoglobin and cell volume which we obtained were higher than most of those previously reported, while the number of red blood cells was higher only as compared with the averages of Haden, Walters, and Foster and Johnson. As a result, our figures for mean corpuscular hemoglobin and for mean corpuscular

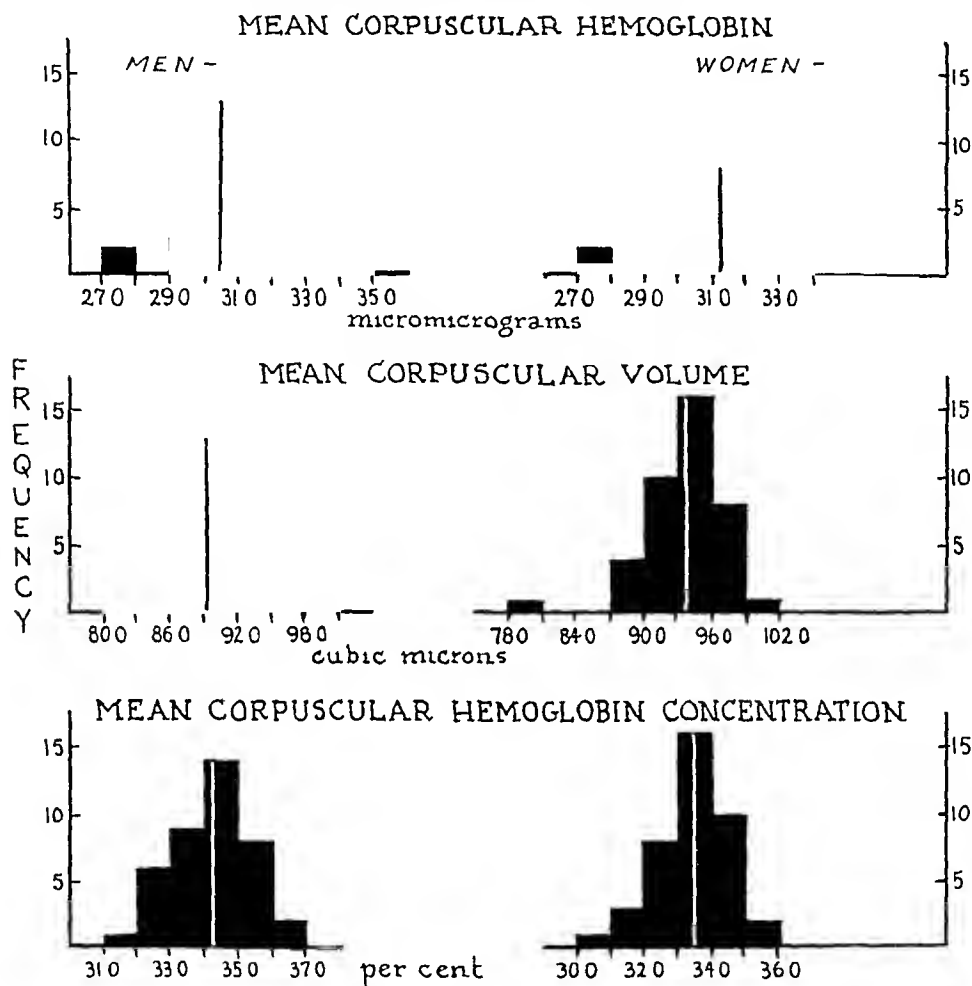


Chart 2—The mean corpuscular hemoglobin, mean volume and mean hemoglobin concentration of the corpuscles of the venous blood of forty normal men (left) and of forty normal women (right). The white line indicates the arithmetic mean.

The mean corpuscular hemoglobin for the men was 30.5 micromicrograms  $\pm 0.15$ , the standard deviation was  $1.4 \pm 0.1$ , and the coefficient of variation was 4.5 per cent. For women, the mean corpuscular hemoglobin was  $31.2 \pm 0.16$  micromicrograms, with a standard deviation of  $1.5 \pm 0.12$  and a coefficient of variation of 4.9 per cent.

The mean corpuscular volume for men was  $89.2 \pm 0.38$ , with a standard deviation of  $3.6 \pm 0.27$  and a coefficient of variation of 4 per cent. For women the mean corpuscular volume was  $93.3 \pm 0.39$ , with a standard deviation of  $3.6 \pm 0.27$  and a coefficient of variation of 3.8 per cent.

The mean corpuscular hemoglobin concentration for the men was 34.2 per cent  $\pm 0.12$ , with a standard deviation of  $1.2 \pm 0.09$  and a coefficient of variation of 3.4 per cent. For the women it was 33.4 per cent  $\pm 0.11$ , with a standard deviation of  $1.1 \pm 0.08$  and a coefficient of variation of 3.2 per cent.

volume were higher than the general averages given by Wintrobe, with many of the individual values considerably above his upper limits of normal. The volume of the individual corpuscles of the women of our series was significantly greater than that of the men. A similar difference between the red blood cells of the two sexes was noted by Osgood and Haskins<sup>2b</sup> in their series.

Our average of 91.2 cubic microns for the two sexes falls about midway between Wintrobe's general average of 86.7 and Huitado's

TABLE 5—*Comparison of the Data Obtained by Wintrobe with Those from the Present Study*

	Men				Women			
	Mean	Range*	Maximum	Minimum	Mean	Range*	Maximum	Minimum
Red blood cells								
Wintrobe, <sup>4</sup>	5.4	4.6 to 6.2			4.8	4.2 to 5.4		
Mugrage and Andresen	5.42	5.16 to 5.68 (in 72.5%)	4.83	6.07	4.63	4.48 to 4.78 (in 80%)	4.41	5.00
Hemoglobin								
Wintrobe, <sup>4</sup>	16.0	14.0 to 18.0			14.0	12.0 to 16.0		
Mugrage and Andresen	16.54	15.7 to 17.3 (in 67.5%)	15.0	18.3	14.45	13.8 to 15.1 (in 72.5%)	12.7	15.7
Volume of packed cells								
Wintrobe, <sup>4</sup>	47.0	40.0 to 54.0			42.0	37.0 to 47.0		
Mugrage and Andresen	48.35	46.1 to 50.5 (in 70%)	43.8	53.6	43.22	41.4 to 45.0 (in 72.5%)	37.1	46.1
Mean corpuscular volume								
Wintrobe, <sup>22</sup>	86.5	82.0 to 92.0 (in 85%)			87.0	82.0 to 92.0 (in 85%)		
Mugrage and Andresen	89.2	85.6 to 92.8 (in 77.5%)	81.3	99.6	93.3	89.7 to 96.9 (in 80%)	79.4	99.5
Mean corpuscular hemoglobin								
Wintrobe, <sup>22</sup>	29.2	27.0 to 31.0 (in 88%)			28.8	27.0 to 31.0 (in 88%)		
Mugrage and Andresen	30.5	29.1 to 31.9 (in 77.5%)	27.2	34.0	31.2	29.7 to 32.7 (in 77.5%)	27.1	33.9
Mean corpuscular hemoglobin concentration								
Wintrobe, <sup>22</sup>	33.7	32.0 to 36.0 (in 86%)			33.4	32.0 to 36.0 (in 86%)		
Mugrage and Andresen	34.2	33.0 to 35.4 (in 67.5%)	31.9	56.8	33.4	32.3 to 34.5 (in 80%)	30.9	35.5

\* Figures for our series represent the limits of plus and minus one standard deviation from the mean and the percentage of individuals falling within these limits.

figure of 96.2 cubic microns for persons living in high altitudes. However, when one takes into account the reports given in table 4 one notes that Haden's average of 91.7 cubic microns for both sexes is a little higher than ours. Foster and Johnson's figure of 88.7 cubic microns for men at New Orleans is only slightly lower than our value of 89.2 for men. The difference between the corpuscular volume in our series and that given by Wintrobe as the world average cannot be explained, therefore, on the basis of the effect of altitude. It seems to suggest at least a variation in the corpuscular volume, which may require the use of regional standards.

Our figures for mean corpuscular hemoglobin concentration are almost identical with Wintrobe's general average and with most of the values previously reported. Further confirmation is given to previous observations that the value for this factor is remarkably constant in the blood of normal persons.

#### SUMMARY

Previous reports of values for the hemoglobin content, the volume of packed cells and the number of red blood cells of the venous blood of normal adults have been made almost entirely from regions not more than 1,000 feet (304 meters) above sea level.

Information regarding the venous blood of forty normal white men and of an equal number of normal white women living at an altitude of about 5,000 feet (1,520 meters) is given in the present study. Determinations of the number of red blood cells, the volume of packed cells and the amount of hemoglobin, figured from the oxygen capacity, are reported for two hundred and forty samples. Corpuscular constants obtained from these values are discussed. The close agreement between the average values for hemoglobin obtained by three methods is shown.

The mean value for hemoglobin of 16.54 Gm per hundred cubic centimeters of blood for men and 14.45 Gm for women and also the mean packed cell volume of 48.35 cc per hundred cubic centimeters of blood for men and 43.22 cc for women are somewhat higher than values generally reported in other parts of the country. The mean red blood cell counts of 5,420,000 per cubic millimeter for men and 4,630,000 for women are about the same as the general average compiled by Wintrobe.

The value for mean corpuscular hemoglobin of 30.5 micromicrograms for men and 31.2 micromicrograms for women as well as the mean corpuscular volume of 89.2 cubic microns for men and 93.3 cubic microns for women are higher than Wintrobe's general average.

Figures for mean corpuscular hemoglobin concentration of 34.2 per cent for men and 33.4 per cent for women further confirm previous observations of its constant value in normal human blood.

# PRIMARY IDIOPATHIC THROMBOPHLEBITIS

NELSON W BARKER, M D

ROCHESTER, MINN

Thrombophlebitis may occur as a primary disease in healthy, active persons who otherwise are normal. In a series of one thousand and eleven unselected consecutive patients with thrombophlebitis of all types seen at the Mayo Clinic in a five year period, seventy-nine formed the basis for the study under discussion. The patients had no evidence of constitutional disease, such as carcinoma or arthritis. They had not undergone surgical operation or childbirth recently and had not recently had a specific infectious disease. They did not have recognizable disease of the heart or dyscrasia of the blood. There was no history or evidence of gross mechanical trauma or of local infectious or suppurative processes in the region of the veins. The patients had not had previous disease of the veins, such as varix. They were examined carefully for occlusive disease of the peripheral arteries, but this was not found. In other words, known causes of thrombophlebitis and conditions in which thrombophlebitis is sometimes seen as a complication were not present, and there was no recognizable factor of abnormal venous stasis.

## HISTORY

In 1845 Jadioux<sup>1</sup> reported a case in which thrombophlebitis of the left femoral vein affected an otherwise healthy man aged 20. It occurred in three separate episodes in four months, without fever or other constitutional disturbance. In 1864 Fiémy<sup>2</sup> reported a case in which thrombophlebitis affected an otherwise healthy man of 56. It apparently involved the popliteal and the long saphenous vein of the left leg in a series of episodes. Sir James Paget<sup>3</sup> wrote in 1866 that there was a type of thrombophlebitis not associated with trauma, exhaustion, infectious disease, local inflammation, pyemia, puerperium or varicosity, which affected patients who had gout but also affected patients with "gouty inheritance" who did not have clinical gout. He described frequent recurrences, mainly in the lower limbs, affecting the superficial rather than the deep veins, and said that the lesions appeared to migrate or jump from one vein to another and usually involved both legs. He

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From the Division of Medicine, the Mayo Clinic

1 Jadioux, quoted by Briggs<sup>5</sup>

2 Fremy, quoted by Briggs<sup>5</sup>

3 Paget, James. On Gouty and Some Other Forms of Phlebitis, St Barth Hosp Rep 2 82, 1866



noted that the affected superficial veins were palpable and hard, that occasionally the deep femoral vein also was involved and that the attacks were accompanied by only slight fever or constitutional disturbances. He observed that some veins subsequently became pervious while others were permanently obstructed. He described the development of collateral veins in some cases and stated that pulmonary embolism was rare according to his experience, since he had observed only three cases of nonfatal embolism, in one of which fatal embolism subsequently occurred.

A similar syndrome was described in 1894 by Daguillon,<sup>4</sup> who reported five cases and reviewed seven others. He expressed the belief that the disease was the result of a diathetic influence, an arthritic but nongouty constitution. He found a high incidence of pulmonary embolism, which was present in six of the twelve patients, three of whom died. In 1905 Briggs<sup>5</sup> stated that there was a disease which had to be classified as "idiopathic recurrent thrombophlebitis," and he cast considerable doubt on the gouty or arthritic origin in the cases reported by Paget and Daguillon. He expressed the opinion that the condition primarily was phleboscclerosis resulting from an anatomic constitutional fault. Subsequently a number of such cases have been reported as instances of "phlebitis migrans" or "thrombophlebitis migrans." This term, for the two may be considered as one, is a rather good descriptive name but has no etiologic significance as it has been applied to a number of secondary as well as primary types of recurrent peripheral and visceral phlebitis. It has never had a clearcut definition. The term was first used by Neisser<sup>6</sup> in 1903 to describe a type of superficial phlebitis occurring in syphilis. Schwarz<sup>7</sup> in 1905 described two cases of phlebitis migrans (nonsyphilitic) in which the condition was associated with advanced tuberculosis. Buerger<sup>8</sup> in 1909 emphasized the association of thrombophlebitis migrans and thrombo-angitis obliterans and the necessity for examining patients who have thrombophlebitis migrans for existent evidence of arterial disease and of watching for future development of arterial lesions. Herrick<sup>9</sup> in 1911 described a

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4 Daguillon, quoted by Briggs<sup>5</sup>

5 Briggs, J. B. Recurring Phlebitis of Obscure Origin, *Bull. Johns Hopkins Hosp.* **16** 228 (June) 1905.

6 Neisser, Ernst. Ueber wandernde Phlebitis, *Deutsche med. Wchnschr.* **29** 660 (Sept. 10) 1903.

7 Schwarz, Gottfried. Phlebitis migrans (nonsyphilitica), *Virchows Arch. f. path. Anat.* **182** 178, 1905.

8 Buerger, Leo. The Association of Migrating Thrombophlebitis with Thrombo-Angitis Obliterans, *Internat. Clin.* **3** 84, 1909.

9 Herrick, W. W. Phlebitis Migrans, with Report of a Case, *Am. J. M. Sc.* **142** 874 (Dec.) 1911.

case of phlebitis migrans in which the venous lesions apparently were not associated with any other disease. He thought that it was the result of some unknown toxin and that there was no danger of embolism. He believed there was no thrombosis, but merely periphlebitis.

Since 1911 cases of thrombophlebitis migrans in which the venous lesion was not associated with arterial involvement, preexisting varix, infection or systemic diseases have been reported by Harkavy,<sup>10</sup> Chlumský,<sup>11</sup> Johnson,<sup>12</sup> Moorhead and Abrahamson,<sup>13</sup> Ryle,<sup>14</sup> Collier,<sup>15</sup> Barber,<sup>16</sup> Walker,<sup>17</sup> Hartfall and Armitage,<sup>18</sup> Krieg,<sup>19</sup> and others. The largest series was reported by Kletz<sup>20</sup> and consisted of five cases.

Associated with the venous lesions of the extremities, Harkavy reported involvement of the portal vein, Moorhead and Abrahamson, involvement of the cerebral and mesenteric veins, Ryle, and Hartfall and Armitage, mesenteric and pulmonary infarcts, Barber and Walker, cerebral lesions. The diagnosis in these cases was based on clinical findings and was unproved. Ryle felt that the pulmonary infarcts were the result of local thrombophlebitis of the pulmonary veins and were not caused by embolism.

With regard to etiologic factors in idiopathic recurrent or migratory thrombophlebitis, in addition to the uricogenic theory of Paget and Daguillon's theory of arthritic diathesis, Briggs', of phlebosclerosis and Herrick's, of toxin, Owen<sup>21</sup> stated that the condition was caused by influenza or associated with influenzal epidemics. Ryle, Kletz, and Hartfall and Armitage noted associated foci of infection and cessation

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10 Harkavy, Joseph. Phlebitis and Thrombophlebitis Migrans, *M. J. & Rec* **120** 64 (July 16) 1924.

11 Chlumský, V. Ueber Phlebitis chronica migrans, *Zentralbl. f. Chir.* **54** 75 (Jan. 8) 1927.

12 Johnson, W. R. Recurrent Idiopathic Superficial Phlebitis. Its Significance in Adult Men, *M. Clin. North America* **2** 1559 (May) 1928.

13 Moorhead, T. G., and Abrahamson, Leonard. Thrombo-Phlebitis Migrans, *Brit. M. J.* **1** 586 (April 7) 1928.

14 Ryle, J. A. Thrombo-Phlebitis Migrans, *Lancet* **2** 731 (Oct. 4) 1930.

15 Collier, W. T. Thrombo-Phlebitis Migrans, Involving the Deep Veins of All Four Limbs, *Lancet* **2** 1408 (Dec. 26) 1931.

16 Barber, Hugh. A Case of Thrombo-Phlebitis Migrans, *Brit. M. J.* **1** 281 (Feb. 13) 1932.

17 Walker, A. B. Observations on Thrombo-Phlebitis Migrans with Notes of a Case, *Lancet* **2** 936 (Oct. 29) 1932.

18 Hartfall, S. J., and Armitage, George. Thrombo-Phlebitis Migrans. A Report of Two Cases, *Guy's Hosp. Rep.* **82** 424 (July-Oct.) 1932.

19 Krieg, E. Thrombophlebitis migrans peripherer Venen, *München med. Wchnschr.* **79** 1712 (Oct. 21) 1932.

20 Kletz, Norman. Thrombo-Phlebitis Migrans, *Lancet* **2** 938 (Oct. 29) 1932.

21 Owen, A. W. Thrombo-Phlebitis Migrans, *Brit. M. J.* **1** 690 (April 21) 1928.

of attacks after their removal Harkavy<sup>22</sup> found that the skin was sensitive to extracts of tobacco in two of five cases. In the majority of the reported cases the patient was a young or middle-aged man.

Reports of cases in which primary idiopathic thrombophlebitis occurred as a single episode and affected chiefly the large veins, such as the iliac, femoral, or saphenous vein, are rare in the literature. Such a case, in which death occurred, was reported by Hutchinson<sup>23</sup> in 1850. Another case, in which there was involvement of the right iliac, femoral and popliteal vein, was reported by Dowse<sup>24</sup> in 1879. The patient was obese, and the outcome was fatal. The clinical diagnosis was confirmed at necropsy. Mueller<sup>25</sup> in 1929 reported observations made in a case of idiopathic thrombophlebitis of the femoral vein ten years after the lesion had occurred. During the interval there had been no episodes of thrombophlebitis.

The seventy-nine cases which form the basis for this study are arbitrarily divided into two groups: (1) forty cases in which the thrombophlebitis was of the recurrent type and was similar to that in certain cases reported as instances of thrombophlebitis migrans in which there was no associated disease, and (2) thirty-nine cases in which there was only a single episode of thrombophlebitis.

These two groups will be considered separately as they present certain clinical differences. It is possible that some of the patients who had a single episode of thrombophlebitis will have recurrences in the future, and it is recognized that the interval between episodes in some cases of the recurrent type is rather long.

#### RECURRENT IDIOPATHIC THROMBOPHLEBITIS

*Age at the Onset of the Disease*—The youngest patient was 21 and the oldest 67 years of age. The average age was 40, and 80 per cent of the patients were less than 50. The incidence by decades was as follows: Seven patients were between 20 and 29 years of age, thirteen, between 30 and 39, twelve, between 40 and 49, five, between 50 and 59, and three, between 60 and 69.

*Sex*—Thirty-five patients (88 per cent) were men.

*Race*—The distribution according to race was as follows: Nineteen patients were English, Irish, Scotch or Welsh, ten were German, five were Jewish, three

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<sup>22</sup> Harkavy, Joseph. Tobacco Sensitiveness in Thromboangitis Obliterans, Migrating Phlebitis and Coronary Artery Disease, *Bull. New York Acad. Med.* **9** 318 (May) 1933.

<sup>23</sup> Hutchinson, D. Crural Phlebitis Occurring in the Male, *Northwest M. & S. J.* **7** 339, 1850-1851.

<sup>24</sup> Dowse, T. S. Note of a Case of Thrombosis with Remarks, *Lancet* **2** 268 (Aug. 23) 1879.

<sup>25</sup> Mueller, Robert. Thrombosis of Venous System. Late Physical Effects and Symptomatology with Special Reference to Lower Extremities. *J. Missouri M. A.* **26** 65 (Feb.) 1929.

were Scandinavian, two were French, and one was Dutch. The proportion of Jewish patients (12 per cent) who had this type of thrombophlebitis was a little higher than the percentage of Jewish patients who register at the clinic.

*Occupation*—This was classed as sedentary in twenty-four cases and as active in sixteen.

*History*—Twenty-five patients gave a history of one or more major acute infectious diseases, but none had had thrombophlebitis as a complication or sequela of these diseases.

*Number and Frequency of Episodes*—At the time of their first examination, sixteen patients had had thrombophlebitis for less than a year and nine for more than five years. Twenty-one patients said that they had had episodes at intervals of from a few days to a month, and in some attacks several veins had been affected at one time. Nineteen patients had had more definite single episodes at intervals of from six weeks to four years. One patient had had twenty to thirty such attacks in eighteen years. Five had had only two attacks.

*Site and Nature of the Lesions*—The veins of both legs were involved in twenty-seven cases, those of the right leg alone in nine cases, those of the left

*Incidence of Involvement of Various Veins in Forty Cases of Recurrent Idiopathic Thrombophlebitis*

	Involved at Some Time	Involved Primarily	No Other Veins Involved
Superficial veins of leg	22	12	4
Long saphenous vein	23	15	6
Short saphenous vein	14	8	1
Popliteal vein	5	1	
Femoral vein	12	3	1
Iliac vein	2		
Superficial veins of arm	4		
Median basilic vein	1	1	
Superficial veins of abdomen	3		
Superficial veins of scrotum	1		

leg alone in three cases and those of the right arm alone in one case. The frequency of involvement of the various veins is shown in the table. The superficial veins of the legs were affected alone in four cases, the long saphenous vein alone in six cases, the short saphenous vein alone in one case and the femoral and iliac veins in one case. The femoral vein was primarily involved in only two other cases. In twenty-eight cases small, medium and large veins in various combinations were affected. Evidence of intra-abdominal thrombophlebitis was present in only one case, the condition was progressive and proved fatal. The patient had an attack of severe abdominal pain and melena. Roentgenologic examination of the gastro-intestinal tract did not reveal anything abnormal, and it was assumed but not proved that the patient had mesenteric thrombophlebitis.

The lesions of the superficial and the saphenous veins appeared to be definitely inflammatory in all cases. There were moderate local pain and usually considerable local tenderness during the acute stage. The veins could be felt as firm, indurated cords, and there was visible local rubor. The acute stage lasted for from one to six weeks, during which time most of the patients were at least partially disabled as walking aggravated the pain. The cordlike vein usually could be felt for several weeks after the acute attack. The involved regions were definitely segmental and varied in length from a few millimeters in the superficial veins and a few centimeters in the saphenous veins (fig 1A) to the entire extent, from groin

to ankle, of the long saphenous vein. In four cases the lesions slowly ascended the long saphenous vein, new segments a few centimeters in length being involved one at a time over a period of months. Constitutional symptoms were slight or absent in all but six cases. Five patients had mild fever, with a temperature from 99 to 101 F, and malaise. In the case in which the mesenteric veins were involved there was prolonged fever, the temperature being as high as 103 F, and much prostration, and later severe anemia developed. The patient died, apparently from generalized toxemia.

*Pulmonary Embolism and Infarction*—Acute infarctions of the lung occurred in twelve cases (30 per cent). One of the patients had three episodes, three had two episodes and the other eight had only one episode. Of the seventeen pulmonary infarctions, seven occurred at the onset of clinical thrombophlebitis of the femoral vein, three at the onset of thrombophlebitis of the long saphenous vein, one at the onset of thrombophlebitis of the short saphenous vein, one a week after the onset of thrombophlebitis of the long saphenous vein and one a week after the onset of thrombophlebitis of the short saphenous vein. The other four infarctions occurred two, four, four and six weeks, respectively, after episodes of thrombophlebitis of the femoral vein. Two patients died, with the clinical picture of pulmonary embolism. Each had had two previous episodes of pulmonary infarction. Necropsy was not performed in these cases.

*Focal Infection*—Definite foci of infection were present in thirty-one cases (77 per cent), no foci were found in seven, and no data were available in two. Some patients had more than one focus. The foci originated in infected tonsils in nineteen cases, in infected teeth in eighteen cases, in chronic prostatitis in eight cases, in chronic cervicitis in two cases and in chronic suppurative otitis media in one case.

*Obesity*—Obesity was present in eleven cases (27 per cent).

*Hypertension*—Hypertension of from mild to moderate degree was present in three cases.

*Special Hematologic Studies*—As has been indicated, routine studies of the blood, such as estimation of the amount of hemoglobin, enumeration of erythrocytes and leukocytes and the Wassermann or the Kline test, were made in all cases but did not reveal anything abnormal. In a number of cases a differential blood count, estimation of the coagulation time (Lee's method), enumeration of the blood platelets, estimation of the bleeding time and determination of the sedimentation rate were made both in the course of acute episodes and between episodes. These tests also failed to disclose any abnormality. The plasma coagulability index (Nygaard method)<sup>26</sup> was determined in eleven cases. In eight cases it was normal, and in three it was definitely increased. The clinical significance of this test has not been established as yet, but these data are inserted for purposes of record.

*Local Complications of the Thrombophlebitis*—Persistent edema of an affected leg (fig 1 B) occurred in nineteen cases. This was of mild degree in nine and of moderate degree in ten cases. It occurred in six of nine cases in which obesity was present, in eleven of twelve cases in which the femoral vein was involved, in only two cases in which both saphenous veins were involved, in two of six cases in which the long saphenous vein was involved and in two of five cases in which the short saphenous vein was involved. Secondary varicose veins developed

<sup>26</sup> Nygaard, K. K. Coagulability of Blood Plasma, Proc. Staff Meet., Mayo Clin. 7: 544 (Sept. 21) 1932.

in eleven cases, and ulcers caused by stasis occurred later in four of these. Three patients had pigmentation, and one had dermatitis caused by stasis. Persistent pain in the region of the inflamed veins occurred in nine cases. A definite neurosis developed in three.

*Pathology and Bacteriology*—Portions of acutely involved veins were removed or the entire venous lesion was excised under local anesthesia in eleven of the forty cases. In eight cases these specimens, which were from 1 to 4 mm in diameter, were obtained from the superficial veins of the lower part of the leg.

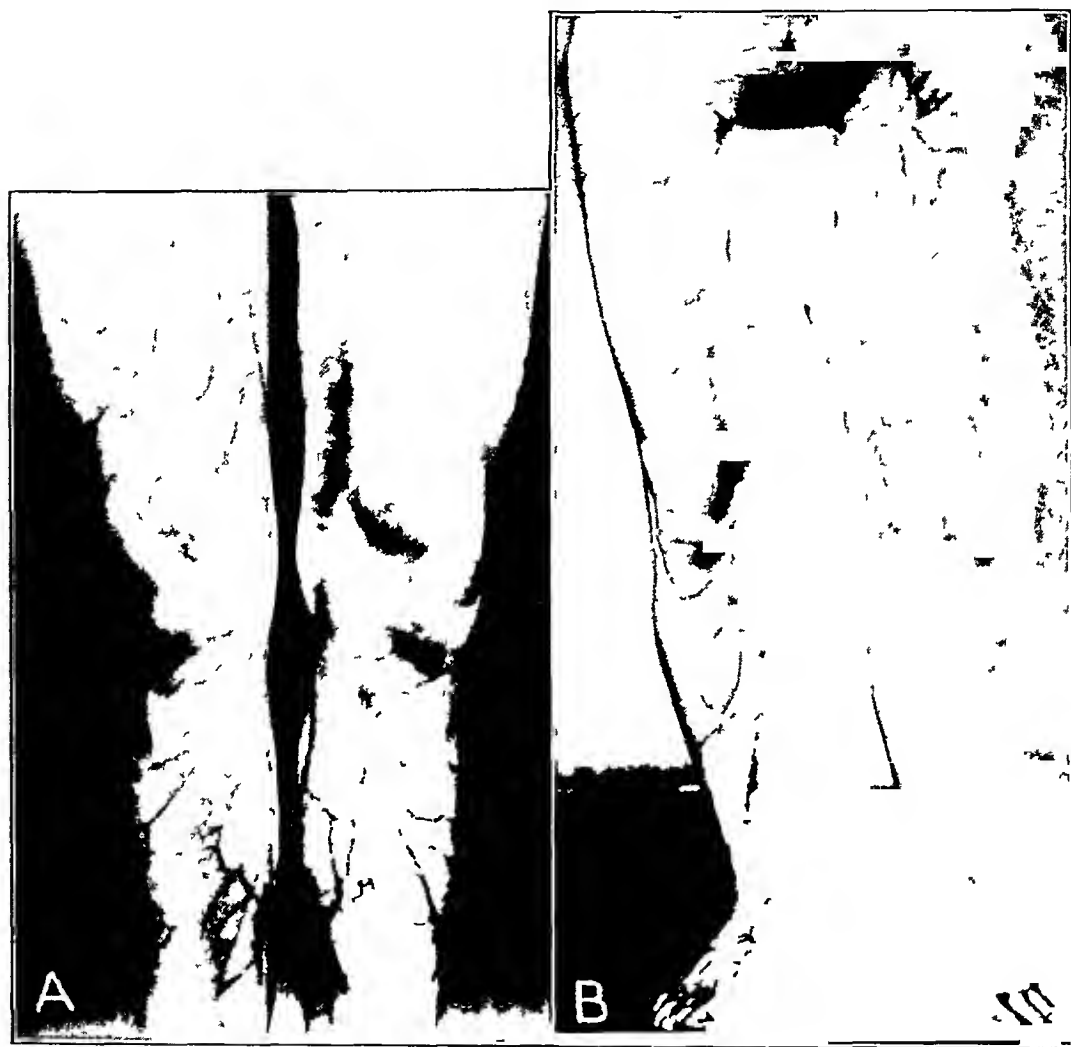


Fig 1—*A*, infra-red photograph showing recurrent idiopathic thrombophlebitis in one of its most common sites, namely, the left long saphenous vein in the lower third of the thigh. The periphlebitis appears as a dark strip with poorly defined markings. The long saphenous vein and its tributaries in the left calf are abnormally prominent as a result of an increase in pressure caused by proximal obstruction. There is no edema. *B*, infra-red photograph showing recurrent idiopathic thrombophlebitis which has involved successively the superficial long saphenous, the femoral and the iliac vein of the left leg, with resultant chronic venous insufficiency and marked edema. The superficial veins of the left thigh are abnormally prominent and distended.

In two cases a portion of the long saphenous vein and in another case a portion of the median basilic vein of the arm was excised. A culture was made from a part of each lesion by Dr T B Magath and Dr Luther Thompson in the following manner. The material was placed in a sterile Petri dish and was then ground in sterile water with sterile sand and a small amount of physiologic solution of sodium chloride. Portions of this solution were placed in tubes of brain broth, some of which were covered with sterile petrolatum. Other portions were put on blood agar plates and incubated both aerobically and anaerobically. Some of the solution was distributed on dextrose-tartaric agar plates and on Sabouraud's culture medium. All the cultures were held for a minimum of one week, and some for three weeks, before being discarded. They were uniformly sterile.

The remainder of the lesions were fixed in a dilute solution of formaldehyde U S P (1:10), embedded in paraffin, cut in sections 7 microns thick and stained

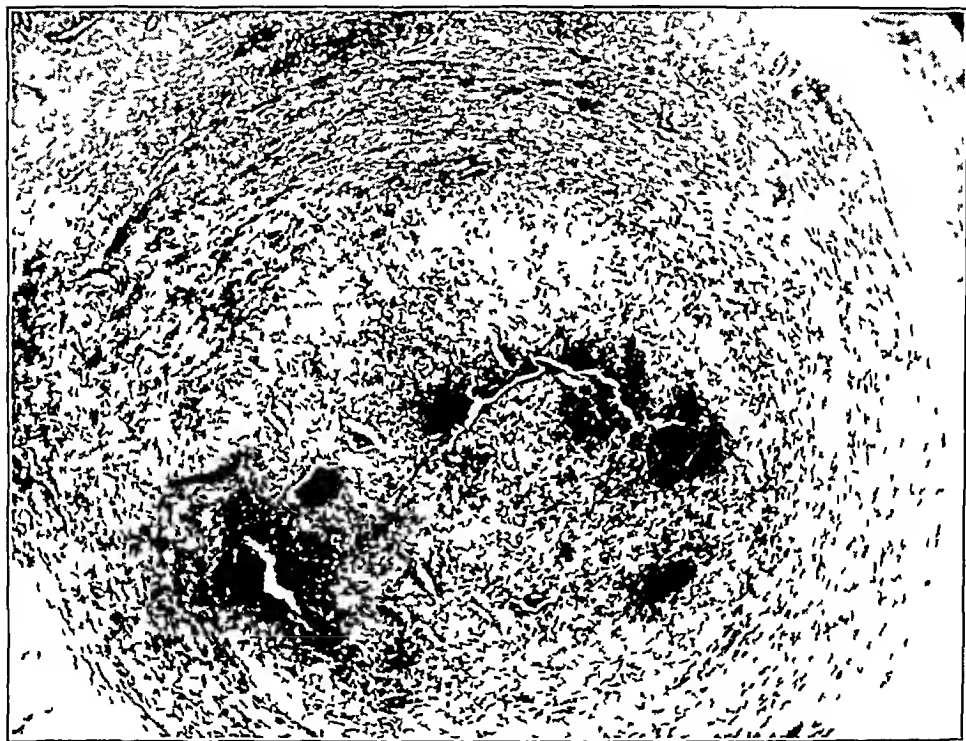


Fig 2—Photomicrograph ( $\times 40$ ) of a section of a superficial vein excised in an acute stage of recurrent idiopathic thrombophlebitis and stained with hematoxylin and eosin. Complete occlusion of the lumen by a cellular thrombus is shown. There is marked infiltration of the wall of the vein and of the perivenous tissue by connective tissue cells.

with hematoxylin and eosin, Van Gieson's stain, and elastin H or Weigert's elastic tissue stain. In all cases the lumens of the veins were occluded. In nine cases the pathologic picture was similar (figs 2, 3 and 4), that is, the occluding mass was made up of well organized tissue, which in some cases contained a few collections of erythrocytes but consisted mainly of connective tissue cells of various types. There were a few lymphocytes, and neutrophilic and eosinophilic leukocytes occasionally were found. In most cases the mass contained a few minute clefts or canals lined with endothelium. The internal elastic lamina was often thickened and partially disrupted. The medial coat of the vein was fairly well preserved but contained a number of small vacuoles. It was heavily infiltrated

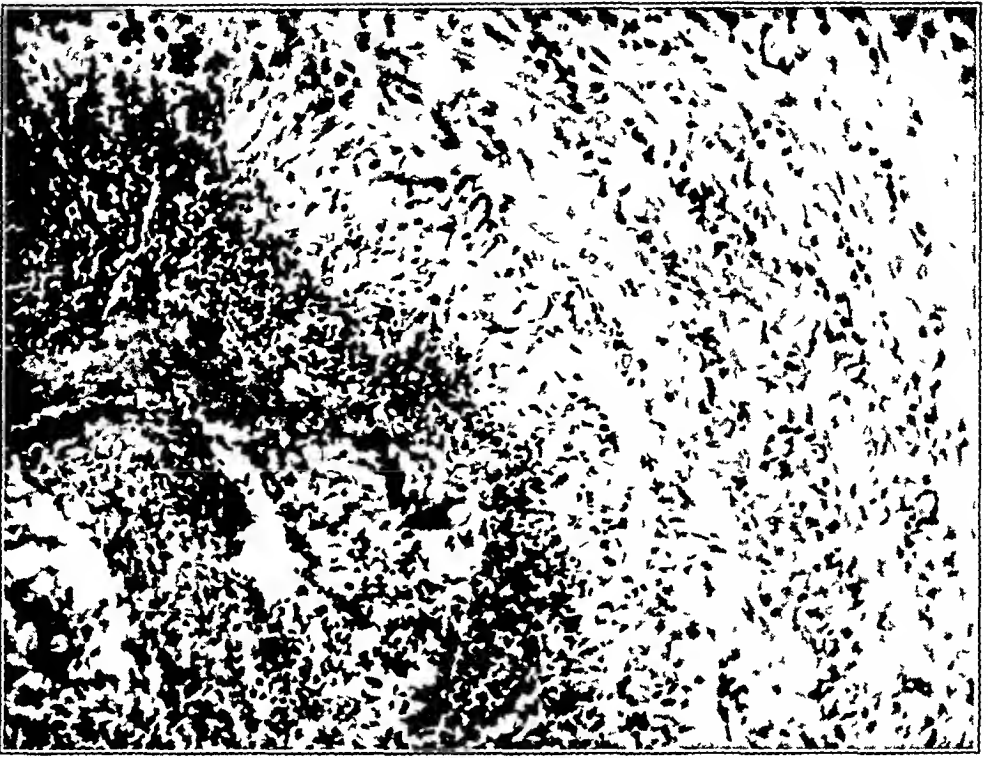


Fig 3—Photomicrograph ( $\times 170$ ) of a section of a superficial vein excised in an acute stage of recurrent idiopathic thrombophlebitis and stained with hematoxylin and eosin. The giant cells in the organizing thrombus, the marked proliferation of the intima and the infiltration of the media may be noted.

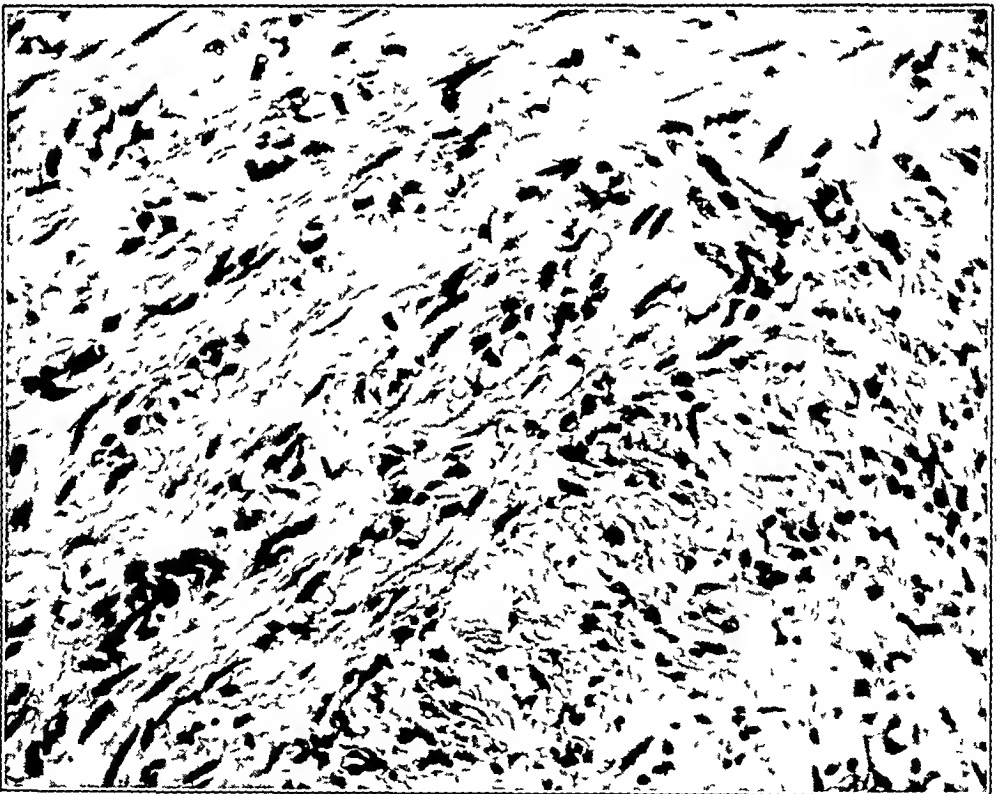


Fig 4—Photomicrograph ( $\times 250$ ) of a section of a superficial vein excised in an acute stage of recurrent idiopathic thrombophlebitis and stained with hematoxylin and eosin. The various types of connective tissue cells and fibroblasts in the organized thrombus and wall of the vein are shown, as well as the edema and vacuolation of the medial coat.



with connective tissue cells and fibroblasts of various types. The adventitia was similarly infiltrated, and often the infiltrating cells extended a considerable distance into the fatty perivenous tissue. Many of the vasa vasorum were surrounded by lymphocytes and fibroblasts. In three cases giant cells were found in the occluding mass. In two cases the entire pathologic picture was somewhat different and showed only a partially organized red thrombus and considerably less infiltration of the media and adventitia with connective tissue cells than was present in the other cases.

This pathologic picture of a vein heavily infiltrated with connective tissue cells and occluded by a cellular mass of connective tissue which sometimes contains giant cells is essentially indistinguishable from the pathologic picture of thrombo-angitis obliterans, except possibly in degree of reaction. Affected veins in typical thrombo-angitis obliterans occasionally are the sites of more dense infiltration with connective tissue cells than those observed in recurrent idiopathic thrombophlebitis.

#### IDIOPATHIC THROMBOPHLEBITIS OCCURRING IN SINGLE EPISODES

*Age*—The youngest patient was 20 and the oldest 69 years of age. The average age was 43. The age distribution by decades was fairly even. Seven patients were between 20 and 29 years old, eight, between 30 and 39, ten, between 40 and 49, eight, between 50 and 59, and six, between 60 and 69.

*Sex*—Twenty-four patients (62 per cent) were men.

*Race*—The distribution according to race was as follows. Twenty-three patients were English, Irish, Scotch or Welsh, seven were German, four were Scandinavian, two were Dutch, one was Italian, one was Slavic, and one was Jewish.

*Occupation*—The occupations of twenty-nine patients (74 per cent) were considered active.

*History*—Twenty-eight patients (70 per cent) gave a history of major infectious diseases, but none of these had had thrombophlebitis as a complication.

*Site and Nature of the Lesion*—Both legs were affected simultaneously in three cases, the right leg was involved in nine cases, and the left leg, in twenty-seven cases. The veins affected were as follows: the femoral vein in eighteen cases, the femoral and iliac veins in seven cases, the long saphenous vein in eight cases, the popliteal vein in three cases, the short saphenous vein in two cases and the external jugular vein in one case. Systemic reactions in all these cases were relatively slight. In fourteen cases there was fever, but the temperature was less than 101 F. There were no chills. In the cases in which the saphenous vein was involved the lesion occurred in long segments only and was associated with moderate pain and tenderness in the vein and slight to moderate evidence of periphlebitis. The clinical picture in the cases in which there was involvement of the femoral and iliac veins was in no way different from that seen in cases of secondary thrombophlebitis in which the same veins are affected.

*Pulmonary Infarction*—This occurred in only three cases and in each at the onset of the thrombophlebitis. The site of the thrombophlebitis was in the femoral vein in one case, in the long saphenous vein in another and in the popliteal vein in the third. Fatal pulmonary embolism did not occur in any of these cases.

*Foci of Infection*—These were present in twenty-two cases but were not found in eleven. The data were incomplete in six cases. The foci originated in

infected tonsils in thirteen cases, in infected teeth in seven cases, in chronic prostatitis in three cases, in chronic cervicitis in two cases and in chronic paranasal sinusitis in one case

*Obesity*—This was present in a rather large number of cases (eighteen, or 46 per cent)

*Hypertension*—In eight cases definite elevation of blood pressure was found

*Local Complications of the Thrombophlebitis*—Persistent edema of varying degree occurred in thirty cases. It occurred in all but one of those in which the femoral or iliac vein was involved, in half of those in which the long saphenous vein was involved and in two of three cases in which the popliteal vein was involved. Secondary varicose veins developed in ten cases. In three of these stasis caused ulcers, in four, eczema, and in one, pigmentation. Persistent pain occurred in ten cases. In seven of these it was at the site of the thrombophlebitis, in two it occurred in the muscles of the calf while the patient was walking, and in one it consisted of nocturnal cramps. Chronic indurative cellulitis developed in one case, osteoporosis of the bones of the foot (partly at least from disuse) in another and a definite neurosis in a third. Biopsy was not performed in these cases.

#### COMMENT

The arbitrary division of these cases of idiopathic thrombophlebitis into two groups according to whether there were multiple episodes or only one is open to question, and it is possible that some of the patients who have had a single episode may have recurrences. However, twenty (more than half) of these patients have been observed for a year and seven for at least five years without recurrences. Only seven of the patients who had recurrent thrombophlebitis had freedom between episodes for as long as a year. There were certain other differences between the two groups. The patients who had single episodes did not reveal any striking similarities as to age, sex or occupation, but did reveal a rather high incidence of obesity. In this group there was rather extensive thrombophlebitis, usually of large venous trunks and less frequently of medium-sized veins. In these respects nonrecurrent idiopathic thrombophlebitis resembles the secondary or complicating types.

The term thrombophlebitis migrans is not used in this paper, as it has been used too loosely in the literature. It is felt that recurrent idiopathic thrombophlebitis, the term used by Briggs, limits the described cases to a definite group and emphasizes the primary character of the venous lesion. Recurrent idiopathic thrombophlebitis is predominantly, although not exclusively, a disease of young and middle-aged men. It is essentially and primarily a disease of small and medium-sized veins. The lesions tend to occur in short segments and appear to be definitely inflammatory. These observations suggest an analogy to thrombo-angitis obliterans, which also is a disease of young and middle-aged men, involves short segments of the vessels and has a definite tendency to recur in episodes. Thrombo-angitis obliterans, however, involves

chiefly arteries, although sometimes it attacks both arteries and veins. It has been mentioned (by Buerger and by Johnson) that the arterial lesions of thrombo-angitis obliterans may develop in cases of migrating superficial thrombophlebitis, and it is possible that some of the patients in the group whose cases are analyzed in this paper may have had early thrombo-angitis without arterial lesions. However, it seems certain that arterial lesions which can be recognized clinically do not develop in most cases of recurrent idiopathic thrombophlebitis. It is not illogical to consider recurrent idiopathic thrombophlebitis as a type of thrombo-angitis obliterans which involves only the veins, just as another type involves only the arteries in certain cases (60 per cent). Thrombo-angitis obliterans, although a definite clinical and pathologic entity, is still an etiologic puzzle. Recurrent idiopathic thrombophlebitis does show some differences from typical thrombo-angitis obliterans with involvement of the veins. The limitations as to age and sex are not so sharp. There is some tendency for recurrent thrombophlebitis to involve large veins (femoral and iliac in 33 per cent of the cases). These veins rarely are involved in thrombo-angitis. Pathologically, there is slightly less proliferation of connective tissue in recurrent idiopathic thrombophlebitis than there is in thrombo-angitis. These may be hair-splitting distinctions.

Like the secondary types of thrombophlebitis, the idiopathic type still presents an unsolved problem in pathogenesis. It reopens the old question of primary phlebitis versus primary thrombosis. In the recurrent types the local inflammatory reaction and the predilection of the lesion for segments of superficial veins are strongly suggestive of a primary lesion of the wall of the vein. However, an increase in tendency to thrombosis might be a contributing factor. A reasonable hypothesis seems to be that the lesions in the veins occur as the result of hypersusceptibility of the venous tissue to injury by toxins or viruses or as the result of the elective localization or affinity of certain toxins or viruses for the venous tissues. There was a rather high incidence of focal infection in the patients observed, and there were certain analogies to other recurrent diseases considered of focal origin.

The question as to whether the pulmonary infarctions are caused by small emboli or localized pulmonary thrombophlebitis cannot be answered definitely without adequate pathologic studies. In the present series evidence of visceral lesions elsewhere than in the lungs was rare. The occurrence of pulmonary infarcts at the onset of the thrombophlebitis, particularly of the large veins, is compatible with the present conception of the occurrence of embolism, namely, that it breaks off when the thrombus is new and before it has had a chance to become organized. Pulmonary infarctions which follow thrombophlebitis that

has been present for several days or weeks may represent the breaking off of a newly propagated thrombus into a larger vein. I feel that the evidence indicates that these infarctions are caused by emboli.

The recognition of idiopathic thrombophlebitis as a cause of transient and prolonged disability and occasionally of death, as well as recognition of its unsolved problems, should be a stimulus to further investigations regarding its cause and pathogenesis.

#### SUMMARY

Idiopathic or primary thrombophlebitis is a definite clinical entity. A study of seventy-nine cases shows that there are two types. First, a recurrent segmental inflammatory venous lesion which tends to involve chiefly small and medium-sized veins and occurs most commonly among young and middle-aged males; second, thrombophlebitis of medium-sized and large veins which is accompanied by less inflammation than is the former lesion and occurs as a single episode without particular preponderance as to age or sex. Recurrent idiopathic thrombophlebitis histopathologically is similar to thrombo-angitis obliterans. Cultures of segments of affected veins which have been obtained for biopsy have shown nothing abnormal. The patients in the series of cases studied revealed a high incidence of definite focal infection in tonsils, teeth and prostate gland. Pulmonary infarction occurred in 30 per cent and fatal pulmonary embolism in 5 per cent. Chronic venous insufficiency of a limb occurred in approximately half of the patients with recurrent and in two thirds of the patients with nonrecurrent thrombophlebitis.

# Progress in Internal Medicine

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## TREATMENT OF POSTOPERATIVE PARATHYROID INSUFFICIENCY

AN INTERPRETATIVE REVIEW OF THE LITERATURE

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AND

AUSTIN C DAVIS, M D

ROCHESTER, MINN

The present paper is limited to a review of the constructive literature which is pertinent to the understanding of the physiologic function of the parathyroid glands, so that patients who have unavoidably suffered injury or destruction of the glands as a result of operation on the thyroid gland may be successfully and satisfactorily treated. The literature on the experimental side is so extensive that only the most important constructive articles can be referred to, and it seems unnecessary to cite more than a few of the early reports, which are of a negative or conflicting nature. Several previous reviews cover the controversial points of these investigations in considerable detail.

The parathyroid glands were first described and named as distinct anatomic entities by Sandstrom in 1880, although, as he pointed out, both Remak (1851) and Virchow (1864) had previously seen and briefly described them in connection with the thyroid gland.

Weiss, in a report in 1881 of the results of thyroidectomy at Billroth's clinic, mentioned tetany as a serious postoperative complication, as did Reverdin (1882) and Kocher (1883). The symptom complex, which Kocher termed "cachexia strumipriva," was as a rule the result not only of thyroid but of parathyroid deficiency. Schiff (1884) demonstrated that after complete removal of the thyroid gland of dogs and cats the animal usually died of spastic or fibrillary contraction and tetany, these experimental observations were confirmed by Wagner (1884), Carle (1888), von Eiselsberg (1890) and others.

However, it was not until 1891 that Gley demonstrated that the tetany which follows thyroidectomy did not occur unless the *glandes thyroïdiennes*, as he preferred to call the parathyroid bodies described by Sandstrom, also were removed. However, as removal of all visible

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parathyroid tissue did not cause fatal tetany in his experimental animals, he was by no means certain that the parathyroid glands were complete physiologic entities. His experimental results were soon confirmed by Verstraeten and Vanderlinden (1894). Vassale and Generali were the first (1896) to show definitely that the removal of all parathyroid tissue, even with the preservation of thyroid tissue, led to fatal tetany, while no tetany resulted if one of the four parathyroid glands remained intact and was capable of functioning, they therefore concluded that the parathyroid glands are not in any way related to the thyroid gland but are special organs possessing a metabolic function of their own, which in some way, still unknown, prevents tetany.

Erdheim, in 1906, by cauterizing the parathyroid glands confirmed the observation that tetany which follows thyroparathyroidectomy is of parathyroid and not of thyroid origin. He went still further and demonstrated that in rats which survived the tetanic convulsion a definite set of trophic disturbances invariably developed more than one month after removal of the parathyroid glands (without removal of the thyroid gland). Typical changes occurred in the incisor teeth, which became soft and elongated and either fell out or were definitely bent. The mouth and gums were the site of gangrenous stomatitis, general cachexia developed, and cataracts formed in the eyes. Erdheim demonstrated, therefore, that tetany in its acute forms is not the only disturbance produced by parathyroidectomy (with the thyroid gland intact) but that definite trophic disturbances are produced.

Thompson and Leighton (1908) exposed, crushed and ligated the parathyroid glands of dogs. Severe tetanic symptoms rarely developed as a result of this procedure, but the animals as a rule passed into a chronic condition of parathyroid insufficiency that resembled the condition which Erdheim noted in rats. This work confirmed Erdheim's suggestion that parathyroidectomy produces chronic and characteristic changes of a trophic nature in addition to, but distinct from, acute post-operative tetany. Thompson and Leighton tried to produce lesion of the parathyroid glands of the type that is likely to follow partial thyroidectomy in man. The study was suggested by Halsted, who stated "It is in the control of hemorrhage that we sacrifice the parathyroid glandules."

The first inkling of the metabolic nature of the tetanic reaction following thyroparathyroidectomy was obtained in 1907, when Parhon and Urechie briefly reported that the intraperitoneal administration of calcium chloride somewhat ameliorates the tetany of experimental animals, although these investigators were unable to prolong the survival of the animals, they found, on the other hand, that the administration of sodium salts aggravates the symptoms.

In 1908 and 1909 MacCallum and Voegtlin demonstrated that there was a marked reduction in the amount of calcium in the serum and the brain after thyroparathyroidectomy and that this was accompanied by violent tetany, which could be completely relieved by the injection of calcium salts. The injection of magnesium salts also seemed to control the tetany, but the effects were confused by the anesthetic and toxic action of the magnesium, while the injection of salts of sodium or potassium tended to intensify the symptoms. These investigators, therefore, concluded that the parathyroid secretion in some way controls the exchange of calcium in the body and thus influences the excitability of the nerve cells. Frouin, in 1909, confirmed the results of MacCallum and Voegtlin and demonstrated that a parathyroidectomized animal could be kept alive indefinitely by continued administration of calcium salts. He emphasized the probable therapeutic value of calcium in clinical cases.

Parhon and Goldstem in 1909 stated that it is well known that a milk diet is beneficial and a meat diet harmful to thyroparathyroidectomized animals and that young animals are more susceptible to tetany than old animals. Their investigation proved that kittens survive thyroparathyroidectomy for a much longer period than usual, provided that they are nursed. The authors suggested that the kittens thereby receive the beneficial effect of a glandular secretion or that the milk so obtained destroys a poison in the gastro-intestinal tract.

Voegtlin and MacCallum (1911) confirmed their original observation that the administration of calcium salts is beneficial in parathyroid tetany, but they also found that the salts of magnesium and strontium have a beneficial effect. They stated that the salts of barium, potassium and sodium are harmful, while ammonium salts have little effect, good or bad. Edmunds (1910 and 1911) demonstrated that a milk diet, which contains considerable calcium, with the addition of extra calcium lactate, reduces to a considerable extent the mortality following thyroparathyroidectomy in dogs.

Greenwald (1911) carried out a balanced experiment in which the intake and excretion of nitrogen and phosphate were determined, and he demonstrated retention of phosphorus (the value for serum phosphate was not determined) following thyroparathyroidectomy. Binger in 1917 demonstrated that a solution of ortho-phosphoric acid or its sodium salts the alkalinity of which was more than  $p_H$  6 was definitely toxic if administered intravenously to normal dogs, and produced tetany which was associated with a decrease in the value for the serum calcium. Salvesen (1923), while he was unable to obtain any evidence of the harmful effect of moderate amounts of phosphate, proved what had long been suspected, that the calcium in the milk is the beneficial factor in a milk diet. He demonstrated that when the calcium was removed

by precipitation with oxalate, the milk was no longer beneficial in prolonging the life of parathyroidectomized dogs. Luckhardt and Goldberg (1923) demonstrated that if 10 Gm of calcium lactate, dissolved or suspended in water, was administered twice a day by means of the stomach tube and if, in addition, 10 Gm of calcium lactate was mixed with the meat diet, parathyroidectomized dogs usually could be maintained in good condition, however, if calcium phosphate was used, the animals rapidly became worse. Hjort (1925) also demonstrated an important point, namely, that only the soluble salts of calcium are beneficial in the treatment of parathyroidectomized dogs. With the use of a 5 per cent solution of calcium lactate, he demonstrated that the soluble salts are even more efficacious if dissolved in water before administration.

As a result of the curative effect of ultraviolet rays on rickets, as demonstrated by Huldschinsky in 1919, and in latent tetany of infants, as demonstrated by Sachs in 1920 and 1921, Swingle and Rhinhold in 1925 attempted to determine the effects of these rays on parathyroidectomized dogs. The last-mentioned workers demonstrated that if dogs were exposed to ultraviolet rays amelioration of the tetany and prolongation of life occurred as a result of increased absorption and retention of calcium. The value for the calcium in the serum, however, was not materially increased, owing to only a small amount of calcium in the food, as calcium salts were withheld from the standard Cowgill diet. This restriction of calcium salts to a minimum was necessary in most similar experimental work, in order to simplify the problem and to discover the effect, if any, of the experimental substance on the intensity and course of postoperative parathyroid tetany. We wish to emphasize that in the utilization of the results of these experiments by the clinician in an attempt to develop a satisfactory therapeutic procedure such a restriction is not necessary. In fact, in the attempts to determine the effect of cod liver oil, viosterol or parathyroid extract, failure to administer calcium salts has been the basic cause of the poor results of most efforts in the practical treatment of patients who had postoperative parathyroid tetany.

Jones (1926), stimulated by the success of pediatricians in combating rickets and infantile tetany with the use of cod liver oil, studied its effect on the tetany of thyroparathyroidectomized dogs. He found that without the addition of extra calcium salts to the standard diet the administration of 20 cc of cod liver oil for two weeks before operation prevented tetany and greatly prolonged life. Life was even further prolonged if the cod liver oil was administered continuously both before and after operation. No favorable effect was obtained unless the administration of cod liver oil was started before operation. However, the value for the calcium in the serum of the treated animals decreased



as rapidly and as much as the value for the animals which did not receive cod liver oil, and in some instances more. Some of the dogs which survived longest (from three to six weeks) had symptoms of chronic parathyroid insufficiency, which were of a trophic nature.

Brougher (1928 and 1930) confirmed the observation that when cod liver oil is administered daily to thyroparathyroidectomized dogs which are receiving a large amount of milk (calcium) daily and a little meat (phosphorus) twice a week, the animals do much better than dogs which receive calcium lactate instead of cod liver oil. The value for the calcium in the serum of the dogs which were receiving cod liver oil tended to approach the normal, while that of the dogs which were used as controls or even those which were receiving calcium lactate did not increase. The author carried thyroparathyroidectomized animals through estrus, pregnancy and lactation by the addition of cod liver oil to the stock diet, which contained milk. Wade (1929) also reported definite beneficial effects as a result of the use of cod liver oil. On the other hand, Greenwald and Gross (1925 and 1929) stated that they could not see how the beneficial effects which followed the administration of cod liver oil could be attributed, either in their own experiments or in the experiments of Brougher and Wade, to the cod liver oil itself, they offered many other explanations, the most important of which follows: "The opinion is expressed that the effect of cod liver oil, and the administration of parathyroid extract, upon calcium metabolism will be found to vary with the calcium content of the diet, the age of the animal, and the need for calcium in the organism."

In 1924 it was demonstrated independently by Hess and by Steenbock and Nelson that various foods, such as oils, milk and cereals, can be endowed with specific antirachitic properties by exposure to ultraviolet rays. The next year they demonstrated that the substance which undergoes change is a sterol. Windaus and Hess (1926), Hess (1927), Hess and Windaus (1927) and Rosenheim and Webster demonstrated by chemical analyses and spectral absorption tests that the substance activated is ergosterol (a sterol closely allied to cholesterol), which is extracted from fungi, yeast, mushrooms and ergot. It was quickly recognized that this activated sterol possesses properties similar to those of vitamin D in cod liver oil (Hess and Lewis). However, as can be seen in the reviews of Harris (1932, 1933, 1934 and 1935) and Bills and his associates, it is fairly certain that the concentrate of vitamin D which is obtained from cod liver oil is not the same substance and does not have exactly the same properties in biologic assays with various species as the vitamin D of viosterol. Rygh (1935) presented physical and chemical data indicating that the two substances are different, and he recommended that the term vitamin D should be used to refer specifically to the substance occurring naturally in cod liver oil and the term

vitamin D<sub>2</sub>, to the substance which is of vegetable origin and is produced artificially by irradiation of ergosterol. This recommendation has not yet been officially or extensively adopted, in fact, Bills, in a recent review of the multiple nature of vitamin D, stated that there probably are at least six forms of this vitamin. In the United States irradiated ergosterol is known as viosterol<sup>1</sup>. Calciferol is the name of a British preparation of pure crystalline vitamin D, 1 mg. of this preparation is four times as active as crude irradiated ergosterol. Space prohibits a review of the literature on vitamin D, and we can only point out that the difference in the effects of cod liver oil and of viosterol in cases of parathyroid insufficiency may be attributed partially to the fact that the cod liver oil contains vitamin A as well as vitamin D, while viosterol contains only vitamin D in a concentrated form, and partially to the fact that the vitamin D of cod liver oil probably is not identical with the vitamin D<sub>2</sub> of viosterol. Further, the toxic properties of various preparations of irradiated ergosterol varied considerably until recently, because of differences in the methods of irradiation, the length of exposure and other factors.

A preparation of irradiated ergosterol apparently was first used in 1928 in the treatment of postoperative parathyroid tetany in man and experimental animals by Urechia and Popoviciu, who reported a doubtful or slightly beneficial effect, with slight increase in the amount of calcium in the serum of parathyroidectomized dogs. Brougher also reported good results when this substance was administered in conjunction with calcium lactate in the form of milk, he emphasized the necessity of a regular supply of calcium and pointed out that if the dog did not retain the milk, tetany developed. Stern reported a case in which a patient who had had parathyroid insufficiency for fifteen years was markedly improved by the use of a small dose of a German preparation of irradiated ergosterol three times a day. Demole and Christ (1929) confirmed the value of irradiated ergosterol in the control of tetany following thyroparathyroidectomy on dogs.

Hess, Weinstock and Rivkin in 1928 and 1929 suggested that the administration of vitamin D increases the concentration of calcium in the serum by acting on the parathyroid glands, as viosterol did not control the tetany unless it was administered some time before operation. If administration of viosterol was started after removal of the parathyroid glands, tetany developed. In 1930 the authors demonstrated, however, that if large doses (from one to four hundred times the therapeutic dose) of viosterol were administered, hypercalcemia was produced.

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1 Viosterol is the name used by the American Medical Association Press to designate preparations of irradiated ergosterol (New and Nonofficial Remedies, Chicago, American Medical Association Press, 1935).

in thyroparathyroidectomized dogs They pointed out that the use of large doses of viosterol may cause withdrawal of calcium from the bones, as shown by Shohl, Bennett and Weed, but that the administration of small amounts brings about retention of calcium, as is true of the use of cod liver oil and of direct ultraviolet irradiation They therefore withdrew their earlier interpretation that viosterol is effective only when the parathyroid glands are intact

Reed and Seed (1933) reported on the treatment of ten patients who had postoperative parathyroid tetany with variable but large doses of viosterol and variable but small amounts of calcium lactate or, at times, without calcium All the patients were benefited, but their condition fluctuated greatly, as illustrated by the variation in the value for calcium, from 6.6 to 14 mg per hundred cubic centimeters of serum in one instance These authors concluded that with careful observation a concentrated preparation of viosterol may be safely administered to human subjects in amounts up to 1 cc daily for several days, without danger of the development of a toxic condition

The investigations of Higgins and Sheard (1928), Higgins, Sheard and Wilder and Wilder, Higgins and Sheard are important because these investigators demonstrated that in chickens deprivation of vitamin D, in a degree insufficient to cause rickets, produces hypertrophy and hyperplasia of the parathyroid glands They also referred to the observation of Johnson that the administration of from 5 to 60 minims (0.3 to 4 cc) of viosterol causes a greater degree of calcification of tissue if large doses of parathyroid extract are administered at the same time It is evident from the first of these studies that there is a close relationship between the activity of the parathyroid glands and vitamin D and that in the treatment of postoperative parathyroid insufficiency in man one must be cautious in administering parathyroid extract simultaneously with vitamin D, as the effect of toxic doses of one substance is enhanced by the simultaneous action of the other

Dale, Marble and Marks reported that a British preparation of pure crystalline vitamin D, known as calciferol (1 mg of which has four times the antirachitic effect of ordinary crude irradiated ergosterol), produces hypervitaminosis Therefore they concluded that pure vitamin D, whether given in large doses orally or intravenously, has the same characteristic toxic action on dogs as the crude product They further demonstrated the important fact that complete parathyroidectomy does not prevent or significantly hinder fatal intoxication, at most, it limits the increase in the concentration of calcium to 15 or 17 mg per hundred cubic centimeters of serum instead of to 18 or 19 mg, which is the concentration produced in the serum of dogs with intact parathyroid glands The results of these authors lend no support to the suggestion

that administration of vitamin D in excessive doses promotes secretion of parathyroid hormone or renders the organism more responsive to its action

Other reports appeared on the value of viosterol in the treatment of both experimental and clinical postoperative tetany, in general, more or less benefit was indicated (Jacques, Jones, Rapoport and Hodes and Stacey), while in a few no benefit was reported (Findley). A study of the failures suggests that the unsatisfactory results could usually, but not always, be attributed to one of the following factors: improper dosage, inconsistency of treatment, lack of sufficient readily available calcium in the diet and the presence of calcium, if any, in an insoluble form as the result of excess phosphate or carbonate. Another reason for the conflicting results reported is that viosterol, more than cod liver oil, tends under certain conditions to increase the amount of phosphorus in the serum (Bills, 1935). Harris (1930), Harris and Innes (1931) and Shelling (1932) demonstrated definitely that not only the quantity of calcium in the diet but the ratio of the calcium to the phosphorus is an important factor in the development of hypervitaminosis D with hypercalcemia in normal animals. Shelling (1932) also stated that the calcium and phosphorus content of the diet is important in the treatment of parathyroidectomized rats. The value of diets low in phosphorus and high in calcium in the treatment of parathyroid tetany has been emphasized by Shelling and Goodman (1934), Shelling (1935) and Hoskins.

Holtz and his associates (Holtz, 1927, Holtz and von Brand, 1929, Holtz and Schreiber, 1930, and Holtz, Isemer and Stichnoth, 1931), under the direction of Professor Windaus and his assistants (Windaus and Hess, 1927, and Windaus and Luttringhaus), were among the first to note that very large doses of vigantol (von Brand and Holtz, 1929 and 1931 and von Brand, Holtz and Putschar), a German preparation of irradiated ergosterol, lead to a series of toxic symptoms which some authors have designated hypervitaminosis D and which consist of nausea, vomiting, hematuria, elevation of blood pressure, increase in the amount of calcium in the serum and the deposition of calcium salts in the heart, blood vessels, kidneys and other organs of the body. Holtz searched for a toxic factor as a possible cause of the hypervitaminosis and found that by prolonging the irradiation of ergosterol under certain conditions he could destroy in large part the antirachitic factor, vitamin D, but that the toxic or "calcinose" factor was still present. Holtz and his associates (Holtz, Laquer, Kreitmair and Moll, 1931, and Holtz, Gissel and Grossmann, 1934) carried out extensive investigations on the action of the "calcinose" factor on normal and parathyroidectomized animals and found that it caused a marked increase in the amount of calcium in the serum of normal animals and a marked deposition of calcium

in the organs of the body, in the parathyroidectomized animals appropriate amounts of this factor increased the value for the serum calcium to normal and prevented the symptoms of parathyroid insufficiency

Holtz (1933 and 1934) and Holtz, Gursching and Kraut (1933) announced that a preparation which they called "A T 10" (*antitetanisches Präparat Nr 10*) could be made by the irradiation of ergosterol with a special method. Vitamin D then was removed or destroyed. The remaining mixture of irradiated products was carefully treated, and a purified substance which had a specific effect on calcium metabolism was obtained. They then demonstrated that an extensive series of patients with postoperative parathyroid insufficiency could be treated efficiently with the administration of the proper amount of "A T 10". Holtz, however, emphatically warned against the danger of overdosage and stated that if the clinical treatment is not carefully controlled by frequent determinations of the value for serum calcium, serious toxic symptoms develop. In consequence, "A T 10" so far has been available only to leading European clinicians for use under carefully controlled conditions (editorial in *Lancet* on Treatment of Tetany, Ekblom, Elliott, Hoff, Martini and Heymer, Marzahn, Paggi, Rieder, Snapper, Wendt and Altenburger, and Winterstein). At present, many reports in the literature fully prove its value in the treatment of postoperative tetany, but on account of the danger of toxic effects and the deposition of calcium salts in various organs, the reports all emphasize that this powerful substance can be used only under close supervision and with frequent determinations of the value for the serum calcium. These favorable results are comparable to those which Boothby and Boothby and Rynearson reported in a series of cases of acute and chronic postoperative parathyroid insufficiency, in this series, which will be referred to later in more detail, the patients were successfully treated with calcium lactate in solution and vitamin D in the form of cod liver oil, and, occasionally, small doses of parathyroid extract were administered.

In 1923 and 1924 Hanson presented evidence indicating that a potent acid extract of the parathyroid gland can be obtained. Collip and his associates, in 1925, describe in detail their method of making an active extract. Such extracts increase the amount of calcium in the serum of normal and parathyroidectomized animals and control the immediate effects of postoperative parathyroid tetany.

Greenwald and Gross demonstrated that the administration of large doses of parathyroid extract leads to excessive solution of calcium phosphate from the bones and to an increase in the concentration of both calcium and phosphate in the serum, and they emphasized Collip's warning against any but the most careful clinical use of parathyroid extract. It should be understood that the hypercalcemia which this extract induces is the result not of improved assimilation but of mobilization of calcium

from the bones, which causes loss of calcium from the body. When this extract was administered to normal dogs in doses of 1 cc, from two to three times a day, there was an increase in the value for the calcium of the serum to 20 mg per hundred cubic centimeters, and the dogs died in a few days.

Albright, Bauer, Ropes and Curb and Aub found that the administration of parathyroid extract increases the excretion of calcium and phosphorus in human subjects who are receiving a low calcium diet. Bauer, Albright and Aub demonstrated that the prolonged administration of parathyroid extract to cats results in demonstrable decalcification of the bones, and Hunter and Aub found that, in consequence, it is a valuable agent in the treatment of lead poisoning.

The danger of the use of large, and especially of increasing, doses of parathyroid extract in the clinical treatment of postoperative parathyroid tetany is illustrated by the case reported by Lissner and Shepardson, in which the patient died. Shortly after the report of these investigators, Boothby, Haines and Pemberton reported a case in which, for a short time, overdosage of parathyroid extract seemed to lead to the same unfortunate result, they, however, recognized that the low value for the serum calcium, accompanied by tetany, was probably attributable in part to overdosage with parathyroid extract and in part possibly to the failure of the patient to take the calcium lactate and cod liver oil as directed. As already mentioned, the untoward effect of parathyroid extract results from the mobilization of calcium phosphate in the bones and its rapid excretion. After the easily mobilized calcium phosphate has been used up, larger and larger doses of parathyroid extract apparently are needed to produce an appreciable, but temporary, increase in the amount of serum calcium. In consequence, in the case reported by Boothby, Haines and Pemberton the dose of parathyroid extract was reduced from 750 to 125 U S P units daily, and at the same time care was exercised to see that the patient received with certainty each day 30 Gm, in divided doses, of calcium lactate, dissolved in water, with 30 cc of cod liver oil. The continued administration of calcium lactate and cod liver oil resulted in such marked improvement that the previous harmful effect of large doses of parathyroid extract could not be overlooked, and, conversely, the beneficial effects of calcium lactate and cod liver oil were strikingly evident.

From a consideration of the pertinent facts brought out in this review, the clinical course of tetany following operation on the thyroid gland may be summarized as follows. The complete removal or destruction of the parathyroid glands results in decrease in the total as well as in the ionic concentration of calcium in the blood serum, this is accompanied by gradual increase in the amount of inorganic phosphate in the serum. When the value for the total calcium becomes less than

8 mg per hundred cubic centimeters of serum, tingling sensations develop in the hands and feet, and as the value for the serum calcium continues to decrease, typical carpopedal contractions develop. If the condition is allowed to go untreated, these contractions may become general and extremely painful and may definitely augment the post-operative risk. If laryngospasm occurs, serious obstruction of the respiratory tract may result and superimpose the additional handicap of anoxemia. In fact, the muscles of the larynx and vocal cords may be among the first to show the effects of spasm, especially if the recurrent laryngeal nerve is irritated by pressure from a ligature or similar cause. If the patient survives the acute attack with adequate treatment and, after leaving the hospital, receives inadequate or intermittent treatment, a series of chronic symptoms develop, while the tetanic-like cramps may become less severe and less frequent as the patient becomes partially adjusted to the decrease in the amount of serum calcium. Occasionally, no evidence of tetany develops while the patient is in the hospital, but the condition first becomes evident a few weeks after operation. Such a delay in the appearance of parathyroid insufficiency can be accounted for on the basis of slight injury by pressure at the time of operation. As a result of chronic parathyroiditis, complete destruction of the parathyroid glands and loss of function occur later, as in the dogs described by Thompson and Leighton. The patient may survive for years, especially if he eats food which contains a moderate amount of calcium and little phosphorus.

The patient with chronic parathyroid insufficiency gradually becomes more incapacitated, and in time trophic changes develop in the teeth, nails and skin. He probably no longer has typical parathyroid tetany, but an epileptiform type of convulsion tends to develop. At times, this may last for hours. The patient is irritable and nervous and becomes so weak that he is virtually helpless. Lenticular opacities are likely to develop. The value for the serum calcium is usually less than 6 mg and may be less than 5 mg per hundred cubic centimeters, although occasionally the diet may contain enough calcium and vitamin D to maintain the value for calcium at 7 mg per hundred cubic centimeters. The value for the inorganic phosphate is high, that is, from 4 to 6 mg, and the value for magnesium is likely to be low, from 1.5 to 1.8 mg per hundred cubic centimeters of serum. McLean and Hastings and McLean, Barnes and Hastings described an easy method of determining the ionic concentration of calcium in the serum, this method requires the determination of the total protein in grams per hundred cubic centimeters of serum, in addition to the determination of the total amount of calcium in the serum. For practical clinical work, however, determination of the total calcium content of the serum is sufficient for observation of the effect of treatment on postoperative tetany.

In this review also certain facts are emphasized which are of practical value in their applicability to the clinical management of parathyroid insufficiency. The irritability of the neuromuscular system, which results in frequent tetanic spasms, seems to be dependent in the main on a sudden decrease in the amount of calcium in the serum, although there is no close correlation between the spasms and the total or ionic concentration of calcium in the blood serum. The decrease in the amount of calcium in the serum probably is the result of decrease in the absorption of calcium from the gastro-intestinal tract. The administration of vitamin D either as cod liver oil or as viosterol has been shown to be effective in aiding such absorption. The oral administration of the soluble salts of calcium has been shown to be effective, at least temporarily, in preventing actual attacks of tetany by producing an increase in the amount of serum calcium, which lasts for a short time. Calcium salts do not prevent the development of the late trophic disturbances, on the other hand, the simultaneous ingestion of phosphates interferes with the absorption of calcium, as calcium phosphate, which is relatively insoluble, is formed in the intestine. The simultaneous administration of vitamin D and an excess of soluble calcium salts has been shown to be much more effective for a given dose than the administration of either preparation alone. In addition, a diet of moderately low phosphate content should be recommended, such as is obtained by allowing the patient to have meat and yolk of egg, which contain considerable quantities of phosphorus, only once a day. Parathyroid extract does not demonstrably aid absorption of calcium from the gastro-intestinal tract, but it relieves the acute attacks of tetany, at least temporarily, apparently by liberating calcium and phosphate from the bones and thereby increasing the amount of calcium in the serum. This procedure, of course, cannot be continued long without using up the readily mobilized calcium and necessitating larger and larger doses of parathyroid extract, with increasing ineffectiveness. As can be seen from the recent review of Aub, parathyroid extract as it is now made cannot be considered to be the complete hormone of the parathyroid glands, because no one has been able to demonstrate that it fulfils the requirements of complete replacement therapy as does thyroxin for the thyroid gland. Prolonged administration of parathyroid extract, except possibly in very small doses, is distinctly harmful and dangerous in the treatment of chronic parathyroid insufficiency, although, as Aub pointed out, it may occasionally be of value in cases of acute tetany in association with a decrease in the amount of serum calcium. The antitetanic preparation (A. T. 10) which was described by Holtz has proved exceedingly valuable in the treatment of postoperative tetany in cases in which the patient can be closely supervised and the value for the serum calcium determined frequently. Excellent results have been



reported by German investigators, however, they are no better than the effects of treatment which we have obtained at the clinic without the use of this agent

The therapeutic regimen which most favorably influences the symptoms of postoperative parathyroid insufficiency, recently reported by Boothby and Davis, embraces the following principles (1) the administration of soluble calcium salts in large doses, (2) the use of a diet low in phosphates, (3) the administration of vitamin D in sufficient amount but in such form that overdosage is unlikely, and (4), finally, the occasional administration of parathyroid extract. On the basis of these principles we have developed a definite method of treating patients with this condition. In some of the cases operation was performed at the clinic and in other instances, elsewhere, therefore the duration of the parathyroid insufficiency varied from a few hours to fifteen years. Patients who have followed instructions and have been able to return for re-examination, observation and slight alteration in their medication have almost invariably done well and have experienced little or no trouble except the necessity of taking calcium lactate, cod liver oil (or viosterol) and, occasionally, small doses of parathyroid extract. The treatment which we have adopted has been designed for the two distinct stages: acute postoperative tetany and chronic parathyroid insufficiency.

The immediate treatment after operation should be instituted as soon as the patient complains of tingling and numbness in the extremities or lips or when the first contraction of the hands develops, with or without accompanying laryngeal spasm. This phase of the treatment is simple and consists in having the patient drink 4 Gm<sup>2</sup> of powdered calcium lactate dissolved in about a third of a glass of water. This dose should be repeated every half hour until the patient no longer complains of tingling and no longer has spasm. This amount of calcium lactate, always completely dissolved in water, should be given about every two hours throughout the day and once or twice at night, when the patient awakens. The value for the serum calcium should be determined as soon as the tetany is noticed, but one should institute treatment immediately, without awaiting the report.

Occasionally, it may be advisable to give one intravenous injection of 10 cc of a 10 per cent solution of calcium lactate or calcium gluconate<sup>3</sup> if there has been any delay in recognizing the onset of the tetany or if the patient is in a critical condition. One such injection usually

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2 As powdered calcium lactate is light, this amount is equivalent to about two level teaspoonfuls.

3 A 10 per cent solution of calcium chloride is frequently used, but it is dangerous because a few drops escaping into the subcutaneous tissue may cause necrosis of the surrounding tissue.

relieves the spasm, and the oral administration of calcium lactate must then be started immediately. The administration of cod liver oil in doses of from 5 to 10 cc<sup>4</sup> two or three times daily should be started within twenty-four hours. The continuation of this regimen prevents the development of any symptoms of tetany.

At the end of a week or two, when the patient is entirely out of danger, the administration of calcium and cod liver oil can be discontinued, while the patient is kept under close observation. Frequent estimations of the value for the serum calcium should be made in order to determine whether tetany developed as a result of permanent parathyroid insufficiency or whether the first attack was merely an acute effect of temporary interference with the blood supply of the parathyroid gland.

The treatment for permanent parathyroid insufficiency should be instituted as soon as it is determined that the patient has received irreparable injury of the parathyroid glands. To be satisfactory, the design of such treatment must take into consideration the effectiveness, the cost and the simplicity of application. The treatment necessitates careful and complete instruction of the patient concerning the significance of the situation with which he is faced, as well as the importance of learning and maintaining the regimen outlined.

Of the soluble salts of calcium, calcium lactate is far less expensive than calcium gluconate, it is equally efficacious and should be obtained by the patient in economical quantities. The most highly purified calcium lactate is not necessary, as the presence of a fraction of a per cent of calcium carbonate or even traces of phosphate do no harm, however, the product should not contain appreciable quantities of calcium chloride. The quantity of calcium lactate required in the treatment of tetany varies in the individual case, but usually it is between 20 and 40 Gm daily. This amount can be measured with sufficient accuracy if one assumes that a level standard tablespoonful contains approximately 5 Gm. The calcium lactate should always be administered in solution, and the patient should be given the following instructions on the preparation of the day's supply. A level tablespoonful of calcium lactate is placed in a suitable dish, and warm water is added slowly while the solution is constantly stirred, then more water and another level tablespoonful of calcium lactate are added, and this procedure is continued until the required daily dose is dissolved and the solution is practically clear. If traces of calcium phosphate or carbonate are present, there is a slight residue, from which the clear solution can be decanted and allowed to cool. The patient should be instructed to take a fifth or sixth of the total daily dose immediately on arising in the morning, a similar amount

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4 A teaspoonful of cod liver oil is a little less than 5 cc

three or four times during the day and a dose on retiring. The dose is more effective if taken a little while before a meal than if taken immediately afterward. A few patients find it necessary to take an extra dose during the night if they become restless or nervous. If the patient is to be away from home, he can take powdered calcium lactate with him and dissolve the proper amount for each individual dose. Nearly all well instructed patients are conscientious about taking the calcium lactate regularly, because they quickly learn to recognize the tingling sensation and nervousness which result from omission of even a few doses.

The regular and constant administration of vitamin D in correct doses is as important as the administration of calcium lactate. It is, however, harder to determine the correct daily dose of vitamin D, and it also is more difficult to impress the patient with the necessity of taking this dose regularly. The ill effects of failure to take vitamin D do not develop quickly, and the patient often can get along for several days or a week or more without experiencing enough discomfort to attract his attention to the omission of the vitamin. Administration of vitamin D seems to be more important in preventing the development of the chronic trophic changes than in preventing the immediate neuromuscular excitability, while the latter condition may be controlled for a considerable time by the administration of calcium lactate. The choice of the form of vitamin D is large and lies between cod liver oil, concentrates of cod liver oil, viosterol and halibut liver oil, however, the commercial combinations of these forms had better not be used except under close supervision. As already mentioned, the fish oils contain vitamin A as well as vitamin D, while viosterol contains only vitamin D. It also has been shown that the vitamin D found in cod liver oil is not identical with the vitamin D ( $D_2$ ) of viosterol, and it is not yet known for a certainty whether the forms of vitamin D found in the liver oils of various fishes are identical. It has been demonstrated (Bills) that the vitamin D ( $D_2$ ) of viosterol tends to increase the phosphorus in the serum of an animal relatively more than the vitamin D of cod liver oil when the same degree of protection against rickets is conferred, which probably is undesirable. In spite of the variability of the various preparations of cod liver oil on the market in their absolute and relative contents per gram of vitamin A and vitamin D, we have found it easier to standardize treatment for our patients with cod liver oil than with viosterol. After all, the percentage variability of the vitamin content of the various preparations of cod liver oil accepted by the Council on Pharmacy and Chemistry of the American Medical Association is small as compared to that for viosterol, with its high content of vitamin D and lack of vitamin A. Overdosage of vitamin D is, of course, much more easily obtained accidentally when a concentrated powerful prepara-

tion like viosterol is used. Hypervitaminosis D, with the danger of formation of calcium deposits in various organs, cannot be overlooked. While we have observed one case in which administration of cod liver oil caused mild hypervitaminosis, with nausea and vomiting and an increase in the amount of calcium in the serum to about 13 mg per hundred cubic centimeters, we have never seen any serious complication arise from its use. Halibut liver oil, which has a much higher concentration of vitamin A and vitamin D than cod liver oil, possibly may be of value in the treatment of postoperative parathyroid insufficiency, especially in cases in which the patient has a distaste for cod liver oil. Its value, however, in the treatment of this condition has not yet been extensively tested. In our experience, administration of from 5 to 10 cc of cod liver oil two or three times a day usually has proved satisfactory, and if calcium lactate is administered in conjunction, as already described, most patients are maintained in good condition indefinitely. Less cod liver oil apparently is needed in the summer, when the patient is outdoors in the sun more than in the winter. Overdosage with cod liver oil is comparatively easy to recognize rather early, because the patient's distaste for the oil becomes accentuated, with the development of nausea and vomiting, such distaste, however, should be carefully distinguished from the natural dislike of the oily or fishy taste. Other causes for the nausea and vomiting also must be excluded.

If the patient can be kept under observation for a sufficiently long time, the concentrates of cod liver oil can be tried, but often it is not possible to arrange a period of observation which is long enough. We therefore have felt safer in using standard preparations of cod liver oil.

In the cases in which we have made observations recently, we have not found it necessary to use parathyroid extract. In three or four instances, however, in which the initial treatment consisted of the administration of calcium lactate, cod liver oil and small doses of parathyroid extract, the patients are doing well, or at least reasonably so, and as they cannot return for observation to determine whether the parathyroid extract can be omitted, we have thought it best to suggest no change in the regimen. The amount of parathyroid extract which these patients are taking is comparatively small and does not exceed 0.7 cc daily (usually less), which is equivalent to 70 U S P units.

The symptoms of myxedema may be associated with those of parathyroid insufficiency and thus may complicate the clinical picture if there has been complete thyroidectomy or if thyroiditis has developed in the remaining thyroid tissue. In our series there were few cases in which there were symptoms of both diseases. If myxedema develops, desiccated thyroid gland should be administered in accordance with the standard method of treating this condition. In the absence of positive

evidence of hypofunction of the thyroid gland, there is, of course, no indication for the administration of desiccated thyroid gland

Before one undertakes the instruction of a patient in the permanent management of postoperative tetany, the patient and his family should be told that the tetany is the result of unavoidable injury to the parathyroid glands and that if directions are carefully followed no serious result will occur and about the only inconvenience with which the patient must contend is appropriate medication throughout life. Frankness in discussing the condition is due the patient, and it should never lead to legal difficulties which would be upheld in court, as the accident may occur in the hands of the most experienced surgeon, with the exercise of all possible precautions. The parathyroid glands may be situated abnormally far forward and therefore may come into the field of operation. Only rarely can these tiny glands be seen by the surgeon during the operation.

In our experience this treatment is satisfactory in controlling acute parathyroid tetany and in maintaining in health, comfort and usefulness persons with chronic parathyroid insufficiency. Trophic disturbances, such as the progressive development of lenticular opacities, can be controlled, and in some instances at least improvement occurs. Boothby and Lillie reported a case of chronic parathyroid insufficiency with the development of cataracts, in which, in addition to the usual general improvement, marked increase in visual acuity followed the institution of treatment. Subsequently, the patient discontinued the use of vitamin D because he was of the opinion that it increased his weight, but he continued to take the calcium lactate and small doses of parathyroid extract. After the omission of vitamin D the opacities of the lenses markedly increased. No change was made in treatment, except to insist that the patient consistently take two teaspoonfuls of cod liver oil three times a day. In a year vision was again so improved that he could see to drive his car and enjoy motion-pictures, which he had not been able to do before the institution of treatment.

Recently Boothby and Woltman reported a case of chronic parathyroid insufficiency which provided a convincing demonstration of the effect of treatment on the trophic changes that occur in association with the disease, as well as of the control of the nervous irritability. A summary of the case follows:

A woman, aged 34, primarily complained of the frequent occurrence of cramps in the hands and occasional generalized convulsive seizures, which had gradually increased in severity since she had undergone thyroidectomy eighteen years before. The convulsive seizures had become much more noticeable during the five months prior to admission to the clinic. In addition, there was marked dystrophy of the nails, the Chvostek and Trousseau signs were present, and the patient suffered from marked weakness and nervousness, so that she was completely incapacitated

The value for the calcium of the serum was 4.3 mg, and that for the phosphate, 5.6 mg, per hundred cubic centimeters of serum. After the institution of treatment, which consisted of the administration of 4 Gm of calcium lactate dissolved in water eight times daily and 5 cc of cod liver oil three times daily, there was immediate and striking improvement in the patient's condition. She recovered strength rapidly and in a few days was able to walk for a considerable distance without difficulty. Ten days later the value for the serum calcium increased to 13 mg per hundred cubic centimeters, and the value for the serum phosphate decreased to 2 mg. The value for the serum calcium decreased immediately after a slight reduction in the amount of calcium lactate and cod liver oil administered daily. When the patient was dismissed, after a month's treatment, the value for the serum calcium was 10.5 mg, and that for the serum phosphate, 3.5 mg, per hundred cubic centimeters. The hypercalcemia was attributed to the fact that larger amounts both of calcium lactate and of cod liver oil are necessary to bring the condition quickly under control, and as soon as this is accomplished and part of the body's depleted calcium is restored, smaller doses of calcium lactate and cod liver oil are sufficient to maintain a calcium balance. When the patient was seen five months later, she was in excellent health and had had no evidence of tetany or chronic parathyroid insufficiency during this interval. The value for the serum calcium was normal, indicating that the amount of calcium lactate and cod liver oil the patient had been consistently taking was the correct amount for this person. The atrophic nails had been shed and were being replaced by healthy ones. For the first time since the development of the symptoms of chronic parathyroid insufficiency, she was leading a normal life and was able to perform the duties of a farmer's wife.

In concluding this review we call attention to the promising results of Stone, Owings and Gey in the transplantation of thyroid and parathyroid glands. These investigators adopted the novel idea of implanting grafts of cultures of thyroid or parathyroid tissue grown on artificial mediums to which increasing quantities of the body fluids of the future host were added. It is to be hoped that this method of transplantation will solve the difficulties hitherto encountered in attempts at grafting. Of special interest to the surgeon is the recent anatomic description by Herrman of the parathyroid glands and their relationship to the parathyroid arteries and the hitherto undescribed parathyroid nerves. The inferior parathyroid nerve is a branch of the recurrent laryngeal nerve, and the superior parathyroid nerve arises from the external division of the superior laryngeal branch of the vagus nerve. Both these nerves join the corresponding parathyroid arteries and with them enter the hilus of the parathyroid gland.

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## News and Comment

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### CHICAGO SOCIETY OF INTERNAL MEDICINE

At the annual meeting of the Chicago Society of Internal Medicine held on May 25 the following officers were elected president, Dr Walter L Palmer, vice president, Dr Andrew C Ivy, secretary-treasurer, Dr Clarence F G Brown

### FIFTEENTH ANNUAL SESSION OF AMERICAN CONGRESS OF PHYSICAL THERAPY

The fifteenth annual clinical and scientific session of the American Congress of Physical Therapy will be held on September 7 to 11, at the Waldorf-Astoria Hotel, New York. The program includes many special features sectional meetings in the specialties, symposia on short wave diathermy, hydrotherapy, exercise and electroresection. Fever therapy and the treatment of vascular diseases occupy an important place and will be discussed by prominent workers in the field. The educational aspects of physical therapy and the relationship of physical therapy technicians to physicians and hospital departments will be thoroughly dealt with. Other features include technical and scientific exhibits and a full day of visiting clinics of hospitals, where technic will be adequately demonstrated.

Physicians, their technical assistants and nurses working in institutional departments of physical therapy are urged to attend this important session. It undoubtedly will be one of the outstanding medical gatherings of the year. There will be no registration fee.

## Book Reviews

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**Examination of the Patient and Symptomatic Diagnosis** By John Watts Murray, M D Second edition Price \$10 Pp 1,219, with 274 illustrations St Louis C V Mosby Company, 1936

From time to time attempts are made to simplify the procedure of diagnosis by offering one or another variety of formulary One is told to consult a list of symptoms, obtains cross-references to various pages and finally by an almost automatic procedure learns what ails any particular patient That such a system can ever work, that formulas can ever replace knowledge of disease and clinical reasoning, is a proposition too absurd to require any particular challenge

In the present book the author attempts to simplify diagnosis along these lines Under each organ, the stomach for example, are a great number of questions and answers, such as "Pain at McBurney's point? Appendicitis," or "Has the patient suffered from recurring attacks of pain over a length of time, with intervals of entire relief between the attacks? Answer Chronic periodic gastro-succorrhoea of the primary or secondary form" One need hardly go farther to make clear the futility of such a compendium, indeed "we recall no equal quantity of printed matter which has pleased us less"

**Verhandlungen der deutschen Gesellschaft für Kreislaufforschung VIII Tagung** By Prof Dr E Koch Price, 15 marks Pp 262, with 80 illustrations Dresden Theodor Steinkopff, 1935

This volume contains the transactions of the German Society for the Investigation of Circulatory Disease for 1935 The main topic for discussion was the relation of circulation and respiration A long series of interesting articles are included, many of them containing original material, and such names as Wenckebach and Hochrein indicate the caliber of the speakers The volume is handsomely published, with many illustrations

**Normale und pathologische Physiologie der Bewegungsvorgänge im gesamten Verdauungskanal Teil 1 Methodik, Anatomie, normale Physiologie** By Prof Dr Med Werner Catel Paper Price, 11 50 marks Pp 250, with illustrations Leipzig Georg Thieme, 1936

This book details in monographic form about all that is known in regard to the motility of the gastro-intestinal tract Methods of study, both experimental and clinical, are detailed, with a large collection of excellent diagrams and illustrations

**Blutungskrankheiten** By Dr Heinrich Lehnendorff Price, 3 30 marks Pp 75 Berlin Julius Springer, 1935

This is one of a series of little books for general practitioners The subject of hemorrhagic disease, which at best is difficult, is dealt with briefly but in accord with modern views

## PITUITARY BASOPHILISM (CUSHING'S SYNDROME)

REPORT OF A VERIFIED CASE, WITH A DISCUSSION OF THE  
DIFFERENTIAL DIAGNOSIS AND TREATMENT

R H FREYBERG, MD

PAUL S BARKER, MD

L H NEWBURGH, MD

AND

FREDERICK A COLLER, MD

ANN ARBOR, MICH

In 1932 Cushing<sup>1</sup> described the clinical syndrome of pituitary basophilism, now frequently referred to as Cushing's syndrome. In 1933 he published additional information pertinent to this interesting condition and listed fourteen verified cases reported in the literature. Most of these were originally recorded as examples of multiglandular disease. The significance of the pituitary lesion (if found at the time) was not appreciated.

The general interest in this newly described syndrome is indicated by the increasing number of cases recognized clinically. How many of these clinical diagnoses will be substantiated by pathologic proof time alone will tell. Eight cases - of the typical syndrome of pituitary basophilism in which a basophil adenoma of the pituitary gland was found at postmortem examination have been reported since Cushing's review (1933).<sup>2</sup> The important features of these cases, together with those of a verified case (herein reported) appear in table 1.

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From the Departments of Internal Medicine and Surgery, Medical School University of Michigan

1 Cushing, H. The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism), *Bull Johns Hopkins Hosp* **50** 137 (March) 1932

2 Since these data were compiled, another verified case of pituitary basophilism presenting the clinical syndrome of Cushing's disease has been reported by J H Lawrence and H M Zimmerman (Pituitary Basophilism. Report of a Case, *Arch Int Med* **55** 745 [May] 1935)

3 A case reported by Russell, Evans and Crooke (*Lancet* **2** 240 [Aug 4] 1934) and another by Rutishauser (*Deutsches Arch f klin Med* **175** 640 1933), in which pituitary basophilism was shown to exist at postmortem examination



TABLE 1—*Verified Cases of Pituitary Basophilism Showing the Typical*

Author	Year Reported	Sex	Age at Onset	Duration of Illness, Years	Clinical Observations								
					Obesity	Amenorrhea	Impotence (Sterility)	Hirsutism	Striae	Glycosuria	Basal Metabolic Rate	Blood Pressure	Skeletal Deformation
Kepler and others <sup>61</sup>	1933	F	30	5	Neck, trunk, abdomen	+		+	+	+	-10 -12	160/120	Spine, skull, pelvis, femurs, compression fractures and gibbus
Arbuthnot and neurologists <sup>62</sup>	1933	M	23		Face, abdomen		+		+	+	-28	Hypertension	Skull
Deutsches Arch f klin Med <sup>175</sup>	1933	F	38	4½	Face, abdomen	+		+			-30 -27	Hypertension	
Britishhauser (case 3)	1933	F		Death at 65 years	Head, trunk				+	(?)		Hypertension	+
Quart <sup>1</sup> and Cran <sup>1</sup>	1934	F	24	4	Abdomen, thighs, upper part of arms	+		+	+	0		180/118	+
Russell Evans and Crooke <sup>1</sup>	1934	M	29	2	Face, abdomen		+		+			210/140	
McCracken <sup>1</sup>	1935	M	10	1½	Face, neck, trunk				+	0	-18	154/110	Very thin vertebrae
Wan <sup>1</sup> and Stephen <sup>1</sup>	1935	F	26	4	Head, neck, trunk	+		+	+			160/100	
Levyberg and others	1935	M	12	7	Head, neck, trunk		+		+	0	-3 -12 -24	175/155	+++

*Clinical Syndrome Reported Since Cushing's Review of the Literature (1933)*

Postmortem Observations	Cause of Death	Comment
Basophil adenoma of pituitary gland 0.5 cm in diameter, adrenal glands normal		Autopsy performed elsewhere, pathological study of pituitary gland only reported, at autopsy adrenal glands found to be normal
Basophil adenoma of pituitary gland 0.3 by 0.3 cm, colloid goiter, adrenal glands larger than normal, arteriosclerosis present, slight glomerular capsular thickening		No blood pressure reading, hypertension reported on fundoscopic examination
Basophil adenoma of pituitary gland 0.58 cm in diameter, colloid goiter with adenoma, parathyroid glands fatty, pancreas normal, left adrenal gland very large, right 5.8 cm, combined weight 20 Gm, cortex broad, adenomatous, hyperplastic, gonads showed no follicles, few corpora lutea, arteriosclerosis present, osteoporosis ++	Apoplexy	Fat emboli in lungs
Pituitary gland showed diffuse predominance of basophils with numerous islands of basophils (serial sections), thyroid gland adenomatous, parathyroid glands very large, fatty, pancreas fatty, adrenal glands enlarged, gonads showed small, fibrotic corpora fibrosa, arteriosclerosis present, osteoporosis present with multiple fractures		
Basophil adenoma of pituitary gland 0.5 by 0.5 cm, increased colloid of thyroid gland, parathyroid glands normal, thymus gland small, fatty, pancreas normal, adrenal glands enlarged, combined weight 35.7 Gm, gonads normal, arteriosclerosis present	Purulent bronchitis and empyema	
Basophil adenoma of pituitary gland, thyroid gland distended with colloid, parathyroid glands normal, thymus gland small, pancreas normal, adrenal glands normal, active spermatogenesis, no osteoporosis, vascular degeneration in kidneys, "nephritis renalis, type IV"	"Uremia"	Definite evidence of toxic type of chronic disease (nephritis renalis IV) was cause of death in uremia
Large basophil adenoma of pituitary gland, with degeneration probably caused by roentgen rays, thyroid gland normal, parathyroid glands normal, adrenal glands entirely normal, gonads small, "grossly no decalcification of marked grade"	Death 4 days after appendectomy	Diabetic dextrose tolerance curve, blood cholesterol 176 mg per hundred cubic centimeters
Basophil adenoma of pituitary gland, thyroid gland normal, fatty atrophy of parathyroid glands, thymus glands not found, fatty infiltration of pancreas, cortical hyperplasia of adrenal glands, especially of zona fasciculata, gonads normal, osteoporosis present		
Basophil adenoma of pituitary gland 0.4 cm in diameter, thyroid gland showed abundant colloid, parathyroid glands not enlarged, fatty atrophy, thymus gland very large (85 Gm), much lymphoid tissue, pancreas atrophic, numerous islands, adrenal glands showed marked hypoplasia, no adenoma, gonads small, complete aspermatogenesis, slight arteriosclerosis, osteoporosis +++, moderate subacute glomerulotubular nephritis and nephrosclerosis	Septicemia after exploration of left adrenal gland	Fat emboli found in lungs, marked fatty infiltration of liver

Several observations of unusual interest were made on our patient, and for that reason the case will be reported in detail

#### REPORT OF CASE

*History*—Z K, a 19 year old youth of Polish descent, came to the University Hospital on Oct 27, 1933, complaining of pain in the ankles when standing. At the age of 15 he fell from a moving wagon and suffered a contusion and laceration of the anterior middle third of the left leg. When he began to walk again (after a few days of rest in bed) he noted pain in the arches of the feet and in the ankles. Pain in the extremities became worse, and for four months prior to admission to the hospital it was necessary for him to use crutches to get about.

The patient enjoyed exceptionally good health as a child. No illness could be recalled. Growth and development had been normal until he was 12 years of age, when he began to gain weight rapidly. At the age of 15 he weighed 165 pounds (74 Kg). His weight steadily increased, so that at the time of entering the hospital he weighed 185 pounds (82 Kg). Growth in stature ceased at the age of 15, when he was 60 inches (152 cm) tall. From puberty until two years before admission he had penile erections and seminal emissions, since then there had been impotence and lack of libido. For two years prior to admission epistaxes occurred about once a month, and slight polyuria and occasional nocturia had been noted. For a year he had noted palpitation and shortness of breath on slight activity, and for several months there had been edema of the ankles. His voice remained high pitched. He never shaved, although he occasionally clipped a soft beard with scissors.

*Physical Examination*—The patient was 155 cm tall and weighed 82 Kg. There was marked obesity, which was more noticeable on the face, neck and trunk. The face was round and florid. There were heavy jowls, large breasts and a protuberant abdomen. Over the shoulders, abdomen and lower extremities were numerous purplish striae. Hair was abundant on the scalp, axillae and pubis. A soft down covered his face. There was compound hyperopic astigmatism. The ocular fundi appeared normal. The visual fields were normal. The neck was short and thick. The voice was high pitched. The anteroposterior diameter of the chest was great. The pulmonary fields were clear. The heart was enlarged, the point of maximum impulse and the left border being 11.5 cm to the left of the midsternal line. The blood pressure was 175 systolic and 155 diastolic. There was a thick abdominal panniculus. The penis and gonads were concealed in the pubic fat. The testes were small, about the size of almonds. There was a pigmented scar on the anterior aspect of the middle third of the left leg (site of previous trauma). Slight pitting edema of the ankles was present. The tendon reflexes were normal (figs 1 and 2).

*Laboratory Data on Admission*—The Kahn reaction of the blood was negative. Urinalysis gave negative results. The hemoglobin content was 90 per cent (Sahl). A blood count showed 5,000,000 erythrocytes per cubic millimeter and 11,800

have not been included in this group because the clinical syndrome characteristic of Cushing's disease was not present. Basophil adenomas of the adenohypophysis have been found in cases not showing clinical manifestations of basophilism. Thus, just as in other endocrine glands, notably the thyroid, an adenoma apparently may exist in the pituitary gland without causing any recognizable clinical abnormality. The incidence of adenoma in hypophyses removed during routine autopsies is being studied by one of us (R. H. F.) and will be reported in a separate communication.



Fig 1—The appearance of the head and neck of the patient at the time he entered the hospital

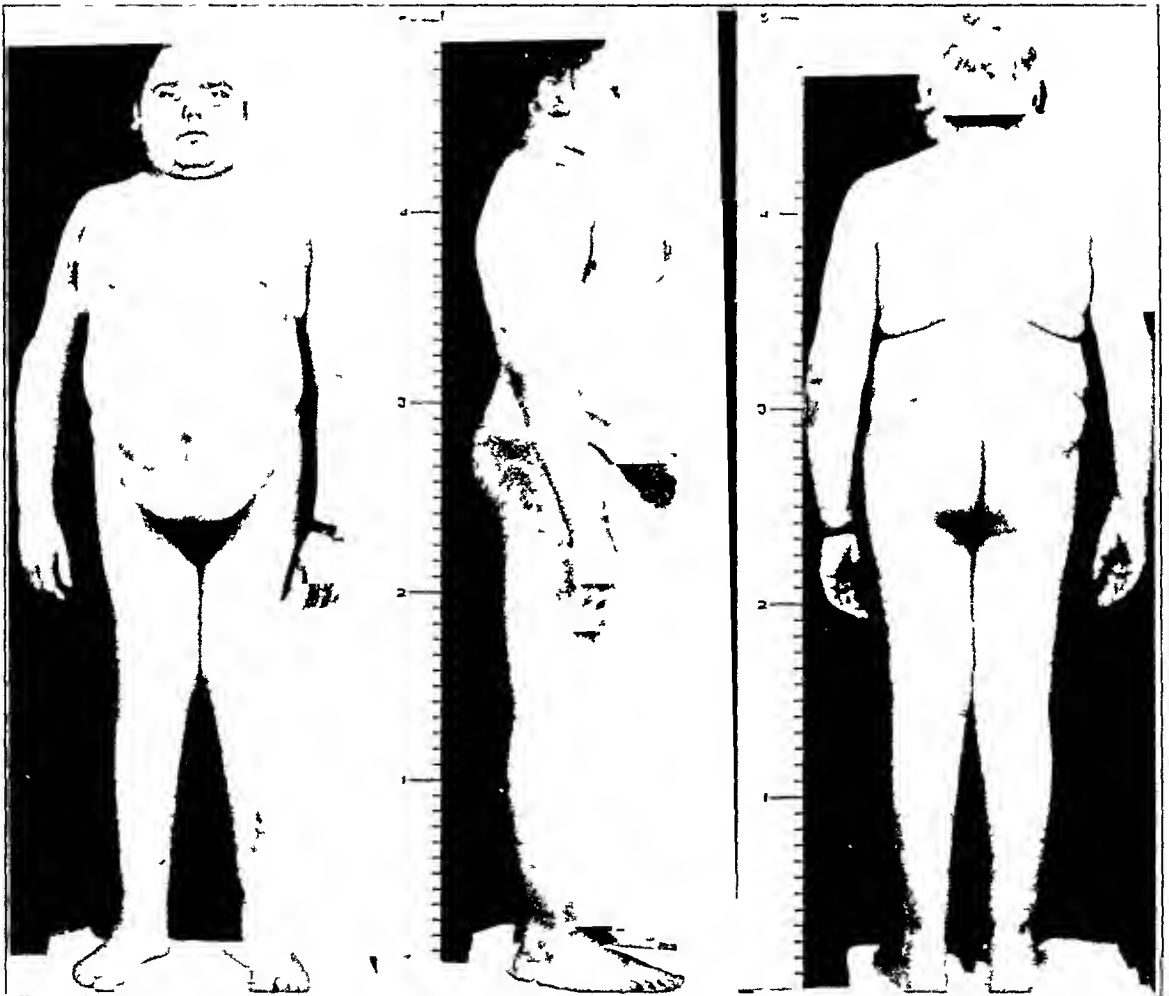


Fig 2—The appearance of the patient at the time of admission

leukocytes The differential leukocytic count was normal Examination of the stool gave negative results Chemical examination of the blood showed nonprotein nitrogen, 30 mg per hundred cubic centimeters, cholesterol, 165 mg (digitonin precipitation method of Windaus), calcium, 112 mg (serum), and phosphorus, 2 mg (serum)

A dextrose tolerance test (150 Gm of dextrose ingested) gave the following results

	Blood Sugar, Mg per 100 Cc	Urinary Sugar
Fasting	83	0
1 hour after ingestion of dextrose	192	0
2 hours after ingestion of dextrose	170	0
3 hours after ingestion of dextrose	107	0

Tests of renal function gave the following results maximum specific gravity of the urine during a Lashmet-Newburgh concentration test, 1.028 (normal 1.029 or above), urea clearance, 80 per cent of the mean normal, phenolsulfonphthalein excretion (6 mg of dye, intravenously), 50 per cent in thirty minutes, 75 per cent in two hours Analysis of the gastric contents showed Fasting, no free hydrochloric acid, thirty minutes after the injection of 0.0005 Gm of histamine hydrochloride, 22 degrees free hydrochloric acid, 30 degrees total acid, one hour, 36 degrees free hydrochloric acid, 46 degrees total acid, two hours, only a trace of free hydrochloric acid The basal metabolic rate was  $-2$  per cent An electrocardiogram showed marked left axis deviation The Ascheim-Zondek test, with a much larger amount of urine than usual, gave negative results Mental tests revealed a mental age of 12 years and 1 month and an intelligence quotient of 81, the classification was dull normal intelligence

*Roentgen Examination* (Dr Carleton B. Pierce)—There were generalized demineralization of the entire skeleton and relative atrophy of all skeletal structures The skull accentuated the relative diminution in the normal amount of calcium The calvarium was very granular The sella turcica was normal The thorax was short and broad The chondral ends of the ribs were somewhat frayed There was a definite widening of the supracardiac soft tissue (suggesting persistent thymus) The pelvis demonstrated well the general decalcification, the bone shadow was no more dense than that of the filled urinary bladder (fig 3) There was incomplete closure of the acetabular junction The acetabular joint spaces were very irregular The head of each femur was conical, that on the right was slightly fragmented The neck of each femur was short and broad, the left showed some buckling The cortex of the tibiae and the fibulae were thin The bones of the ankles and feet showed diminution of calcium content The head of the first right metatarsal bone was flattened, and the head of each second metatarsal bone was fragmented The elbows, forearms and wrists demonstrated delay in union of the epiphyses (fig 4) The spine showed a most striking abnormality There was marked rarefaction, the vertebral bodies had been reduced to an extremely thin meniscus, as a biconcave lens, and the intervertebral disks had swelled, so that they were almost spherical ("fish spine"), there was preservation of the epiphyseal centers of the anterior and posterior margin of the vertebral bodies (fig 5) In summary, the roentgenograms demonstrated marked generalized skeletal decalcification without focal rarefaction and delay in closure of epiphyseal junctions (roentgen age, 15 years or less)

*Course and Treatment*—A diagnosis of "Cushing's syndrome" with a basophil adenoma of the adenohypophysis was made (by P. S. B.) The calcium, phosphorus and energy exchange were studied for a period of five months The results

of these studies are reported in separate papers<sup>4</sup> During this time the patient was fed a reduction diet, supplying 890 calories His weight decreased 22.5 Kg, so that he weighed 60 Kg at the end of this period of study<sup>5</sup>

The patient's condition improved He became able to walk without the use of crutches and with less pain As his weight was reduced, the blood pressure gradually fell, so that at the end of March 1934 it averaged 155 systolic and 125 diastolic Frequent urinalyses during the entire study gave negative results On March 27, 1934, the blood count showed hemoglobin, 80 per cent (Sahl), erythrocytes, 5,300,000, and leukocytes, 12,250 Roentgenograms made on that date demonstrated no essential change in the skeleton



Fig 3—Roentgenogram of the pelvis The degree of decalcification is emphasized by the fact that the pelvic bones are no more opaque to the roentgen rays than the urine-filled bladder

On March 29, 30 and 31 and April 2, 1934, the patient received roentgen therapy to the hypophysis as follows 200 roentgen units (measured in air) was given through two portals 10 by 10 cm (each temporal region) daily, with the central ray aimed at the pituitary fossa (total 1,600 roentgens) The factors were 200 kilovolt peak, 30 milliamperes, 50 cm focal skin distance, a filter of 0.5 mm of

4 Freyberg, R. H., and Grant, R. L. Calcium and Phosphorus Metabolism in a Verified Case of Pituitary Basophilism, *Arch Int Med*, to be published  
Freyberg, R. H., and Newburgh, L. H. A Study of the Obesity and Energy Exchange in a Verified Case of Pituitary Basophilism, *Arch Int Med*, this issue, p. 213

5 Footnote deleted by the authors

copper plus 1 mm of aluminum and 99 milliamperes per minute (each part 33 minutes as prescribed equals 200 roentgens)

The patient was discharged on April 5, 1934, advised to eat a 1,500 calorie diet, rich in calcium and supplemented by 6 Gm of calcium hydrogen phosphate ( $\text{CaHPO}_4$ ) daily. When discharged, he weighed 60 Kg.

The patient returned on May 29, 1934, feeling about the same as at the time of discharge. He had been up and about the house and doing light work about a farm. The findings on physical examination were essentially the same as when he was discharged. The weight was 66.5 Kg. (He had not been able to stay on



Fig. 4—Roentgenogram of one wrist, showing the ununited epiphyses

his diet). The blood pressure was 160 systolic and 130 diastolic. There was slight edema of the ankles.

Laboratory data at that time were as follows. The urine was normal. The hemoglobin content was 75 per cent (Sahli), the erythrocytes numbered 4,050,000 per cubic millimeter, and the leukocytes, 9,800. The stool was normal. Tests of renal function gave the following results: Maximum specific gravity of the urine during the Lashmet-Newburgh concentration test, 1.028, urea clearance, 104 per cent of the mean normal, phenolsulfonphthalein excretion (6 mg of dye intravenously), 26 per cent in fifteen minutes, 68 per cent in two hours. The plasma contained 6.96 Gm of protein per hundred cubic centimeters—albumin, 4.76 Gm, and globulin 2.2 Gm. The albumin-globulin ratio was 2.16. Roentgen examina-

tion revealed further destruction of the head of the left femur, otherwise there was no skeletal change

Calcium and phosphorus studies were carried out over another period of three months, throughout which time the clinical status remained essentially unchanged except for reduction in weight in response to undernutrition (900 calory diet) On Aug 22, 1934, he was again discharged At that time he weighed 58 Kg

The patient returned during the latter part of September 1934 There was no apprecable change in the symptoms or in the results of laboratory tests The



Fig 5—A lateral roentgenogram of the spine, showing the marked decalcification and the thin biconcave vertebral bodies separated by large intervertebral disks (fish spine)

weight was 59.3 Kg The blood pressure was 175 systolic and 135 diastolic During the time this patient was studied, several members of the Mayo Clinic<sup>6</sup>

6 (a) Kepler, E J Polyglandular Dyscrasias Involving Abnormalities of Sexual Characteristics Report of Four Cases, Proc Staff Meet, Mayo Clin 8 102 (Feb 15) 1933 (b) Kepler, E J, Kennedy, R L J, Davis, A C, Walters, W, and Wilder, R M Suprarenocortical Syndrome and Pituitary Basophilism Presentation of Three New Cases, Proc Staff Meet, Mayo Clin 9 169 (March 21) 1934 (c) Walters, W, Wilder, R M, and Kepler, E J The Suprarenal Cortical Syndrome Report of Two Cases with Successful Surgical Treatment, Proc Staff Meet, Mayo Clin 9 400 (July 3) 1934



reported cases of a syndrome similar to that of our patient, in which a cortical adrenal tumor or hyperplasia was found, with cure after the removal of the tumor or of part of the hyperplastic glands. Because roentgen therapy to the pituitary body was followed by no improvement in our patient, it was decided to explore the adrenal glands surgically. Intravenous pyelographs showed no evidence of displacement or distortion of either kidney. On Oct 1, 1934, the left adrenal gland was explored (by F A C). The gland contained no tumor but was thought to be considerably longer than normal. The lateral half was removed. It was felt wise to delay exploration of the right adrenal gland until a later date.

Microscopic examination of the portion of left adrenal gland by Dr C V Weller revealed "A portion of thin, flat adrenal gland, showing hypoplasia of

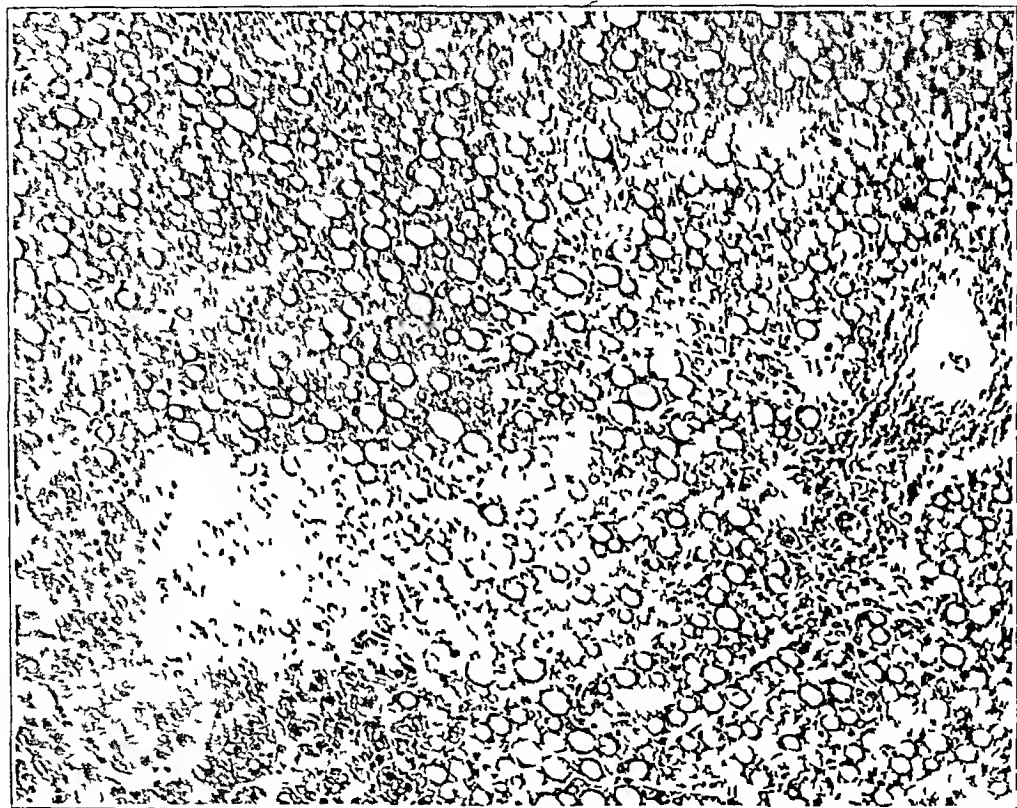


Fig 6—A section of the liver, showing the marked infiltration of fat

the cortex and a reduced medulla. The cortex shows well marked lipoidosis, and there is a small mononuclear infiltration in the cortex. The cortical cells are distinctly smaller than normal. It is not safe to judge functional activity on this ground, however, since the small size of the cells might indicate low output, or, conversely, the cells may be small because of increased rate of output."

Pneumonia developed, and a severe infection with *Streptococcus haemolyticus* spread from the wound through almost the entire abdominal subcutaneous tissue. Septicemia (*Str haemolyticus*) developed. The patient died on Oct 11, 1934.

*Autopsy* (Dr C V Weller)—Besides those concerning the endocrine system, which will be described in detail, the following observations are of interest. The lungs showed extensive fatty embolism. In the liver there was marked fatty infiltration, involving practically the entire lobule (fig 6). There were several small adenomas of the bile ducts. The gallbladder contained three pigmented cholesterol

calculi. The kidneys showed cloudy swelling, deposits of lime salt in the tubules and multiple acute and chronic inflammatory foci, with infiltration by lymphocytes and plasma cells. Glomerulotubular nephritis was present in moderate degree (fig 7). Occasional arterioles showed sclerosis (fig 8).

The abdominal aorta contained patches of intimal lipoidosis and atheromatous plaques. All bones examined showed marked osteoporosis. The vertebrae could be easily cut with a knife. Microscopic examination revealed marked osteoporosis, with fatty marrow. In areas of growth there was a retardation of the transformation of cartilage into bone, with areas of rather cellular cartilage left among the trabeculae of the bone.

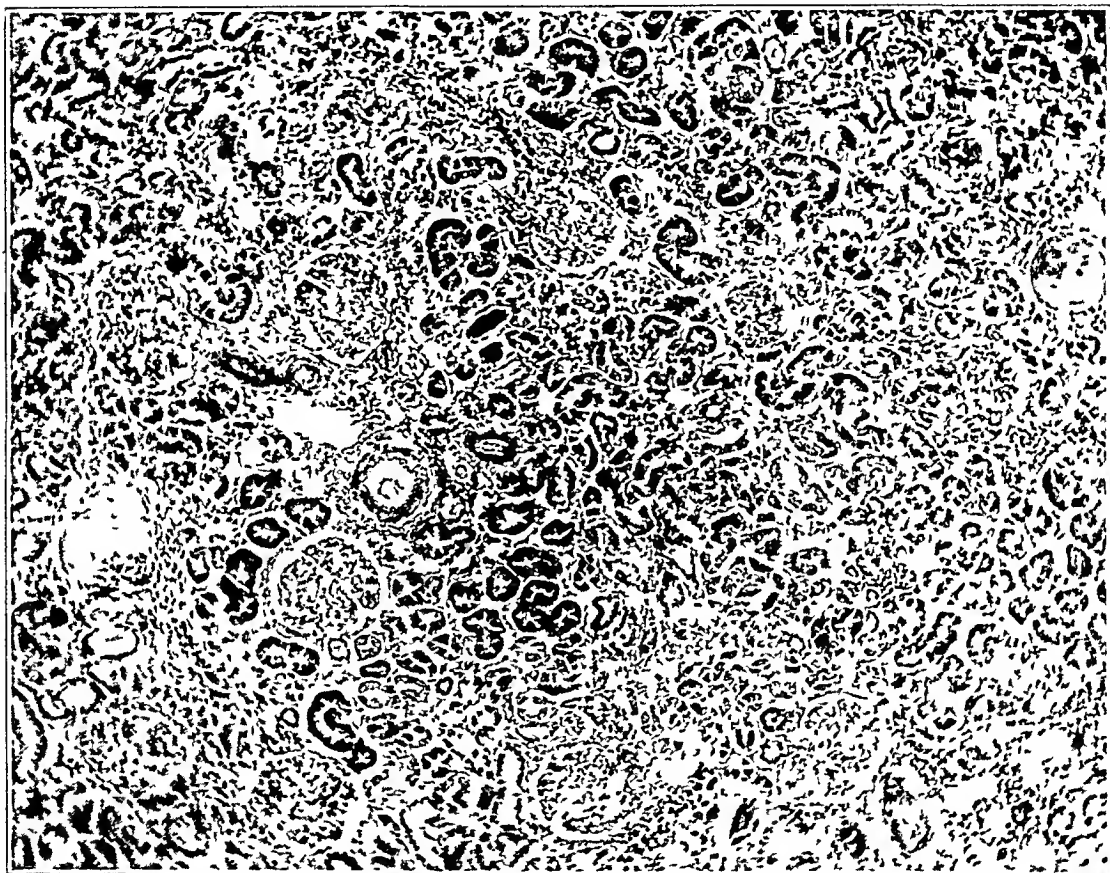


Fig 7—A section of kidney showing scarred glomeruli and areas of cellular infiltration

*The Endocrine System*—The hypophysis was slightly larger than normal. Cut sections showed an atypical grayish-pink cellular area in the anterior lobe, extending into the pars intermedia (fig 9).

Microscopic examination revealed marked congestion. Eosinophils were in slight excess in the anterior lobe. There was moderate edema of the pars nervosa. The atypical cellular area seen in the gross specimen was composed of cells larger than any of the normal cells of the anterior lobe. With Mayer's hemalum (1 Gm hematoxylin, 50 Gm potassium alum, 0.2 Gm sodium iodate and 100 cc distilled water) and eosin the cytoplasm stained purplish blue, whereas eosinophils (in the surrounding portion of the gland) were clearly demonstrated in the same preparation. With special stains, granules were imperfectly demonstrated that tended

toward basophilic. This appeared to be an adenoma of imperfect differentiation, slightly basophilic (figs 10 and 11)

(A portion of the material was sent to Dr Harvey Cushing and Dr Eisenhardt, who gave the following opinion regarding the adenoma) "We think

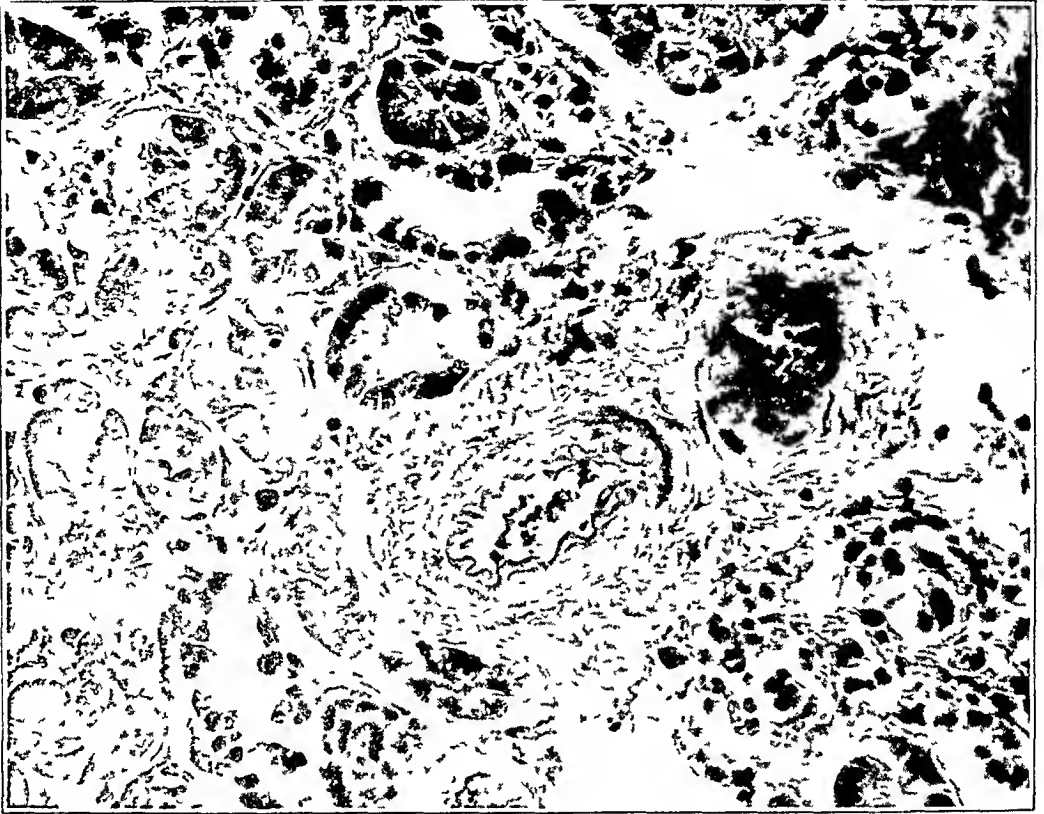


Fig 8—A section of kidney under greater magnification, showing arteriolar fibrosis



Fig 9—The pituitary gland sectioned longitudinally

that the lesion in the pituitary sections you have sent us is a typical basophilic adenoma'

Dr Percival Bailey also examined sections of this gland and allowed us to quote him as saying "It is quite impossible to determine accurately the nature of this tumor because of improper fixation and inadequacy of the material sub-

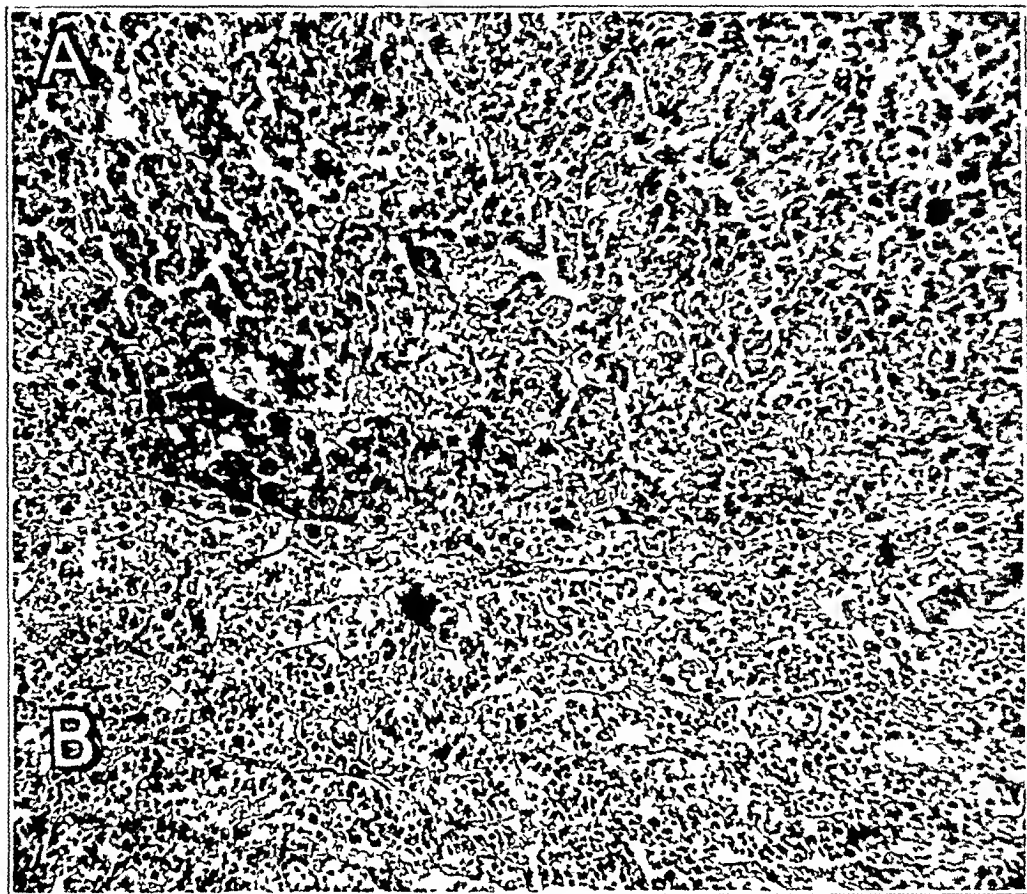


Fig 10—A section across the adenohypophysis, showing (A) the adenoma and (B) the surrounding adenohypophysis

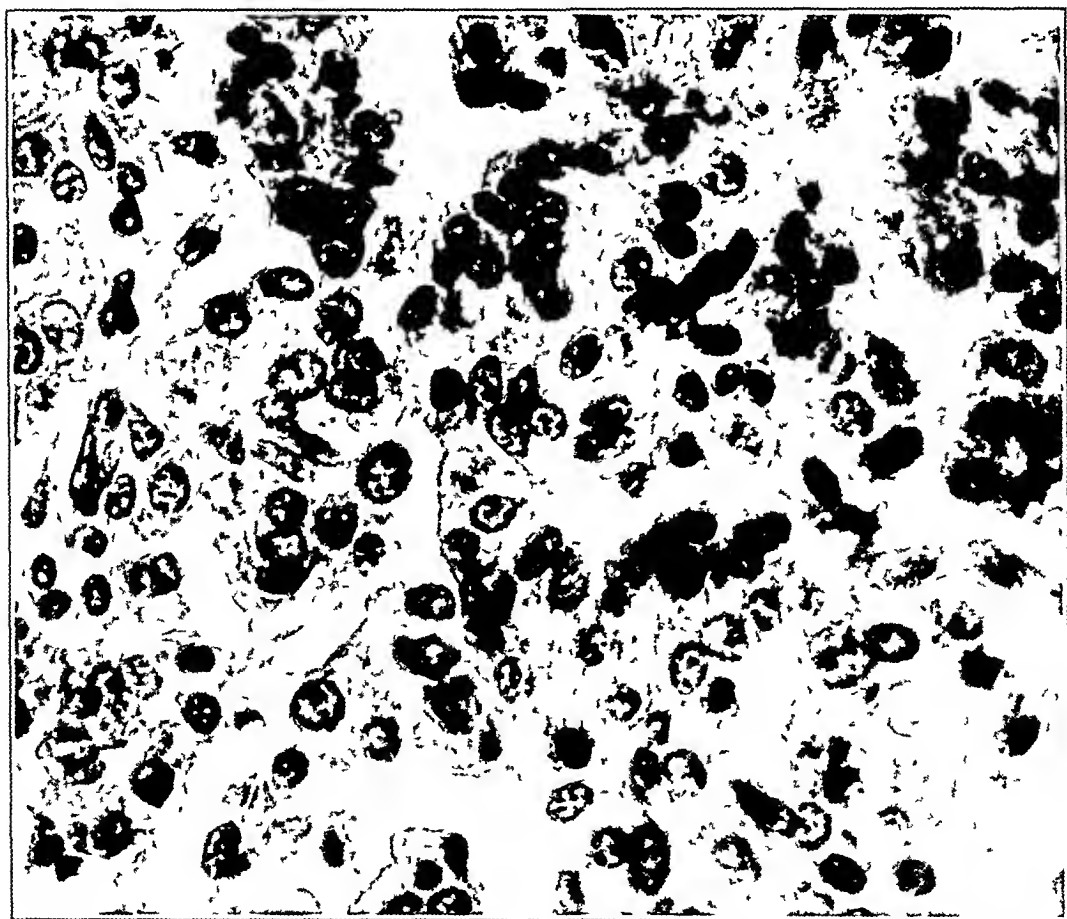


Fig 11—The appearance of the hypophysial adenoma under greater magnification

mitted. However, it is my opinion that the tumor contains a large number of basophilic cells. There are no eosinophilic cells. It is impossible to determine with any degree of certainty the nature of the majority of the cells composing the tumor."

The right adrenal gland measured 5 by 4 by 8 cm. The cortex and medulla were thin, there was no neoplasm.

Microscopic examination revealed marked hypoplasia (fig 12), congestion and infiltration by lymphocytes and plasma cells, particularly in the medulla. There were agonal bacterial emboli.

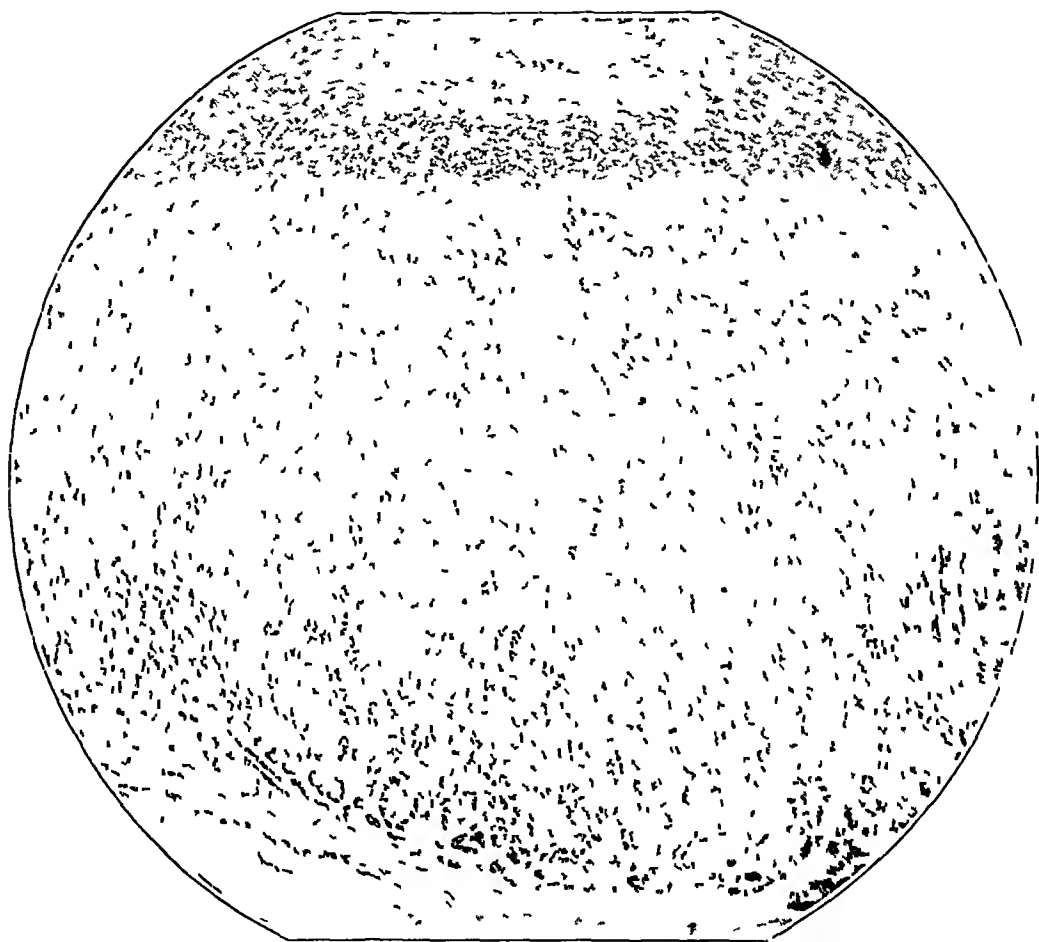


Fig 12—A cross-section of the right adrenal gland under low power magnification, showing the atrophic cortex and the scanty medulla.

The remainder of the left adrenal gland was similar to the right and, in addition, showed surgical hemorrhage and areas of necrosis.

The thymus measured 9 by 6 by 15 cm and weighed 85 Gm (very large for the age of the patient). It was made up of a considerable amount of pinkish-gray lymphoid tissue but little fat, was somewhat nodular and contained no evidence of neoplasm (fig 13).

Microscopic examination revealed very marked lymphoid hyperplasia (fig 14).

The thyroid gland was not enlarged. Colloid was fairly abundant. There was no adenoma.



Fig 13—The thymus as it lay in the thorax. Practically no fat was found in this large fleshy gland.

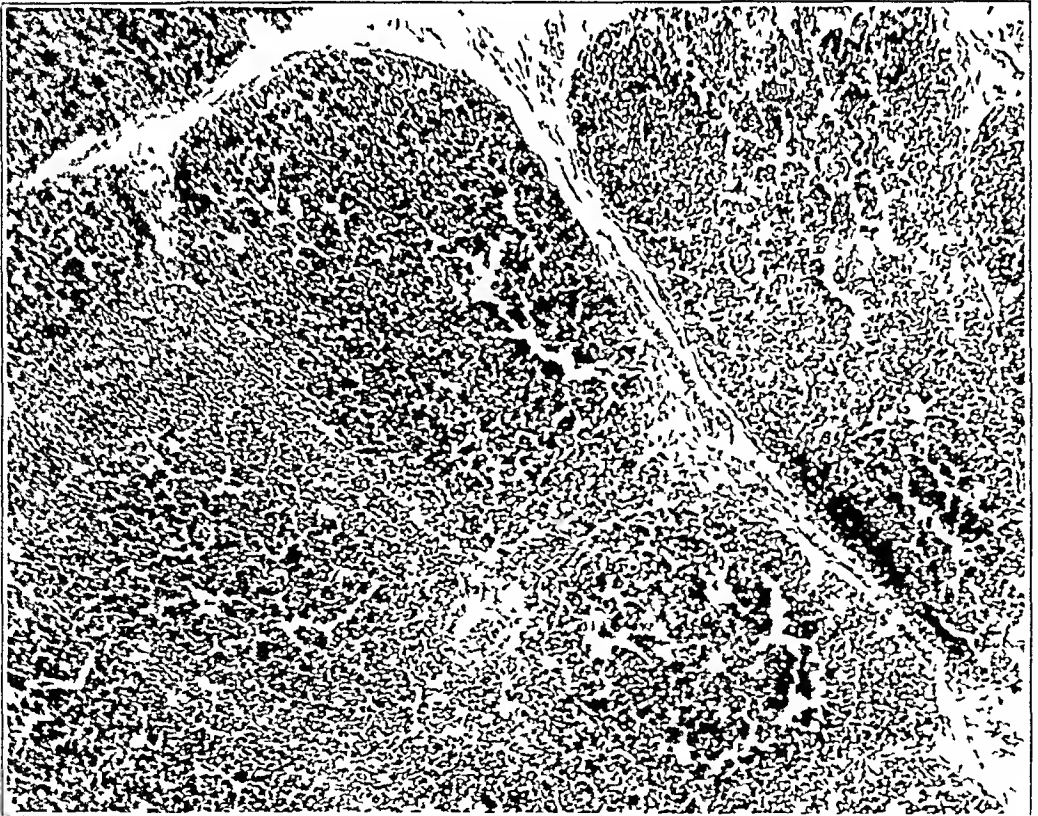


Fig 14—A section of the persistent hyperplastic thymus under low power magnification. Note the lobular architecture and the numerous "thymic corpuscles."



Microscopic examination revealed colloid in normal amount, no adenoma and no evidence of Graves' constitution. Staining for fat showed no lipoidosis of the epithelium.

The parathyroid bodies were not enlarged. The largest of the four dissected was the size of a small pea. Microscopic examination showed advanced fatty atrophy, more than half of the glandular epithelium being replaced by adipose tissue, no adenoma was present (fig 15).

The pancreas was of average size. Microscopic examination revealed fatty atrophy and also simple atrophy of the acini. The islands were numerous and averaged larger than normal (fig 16).

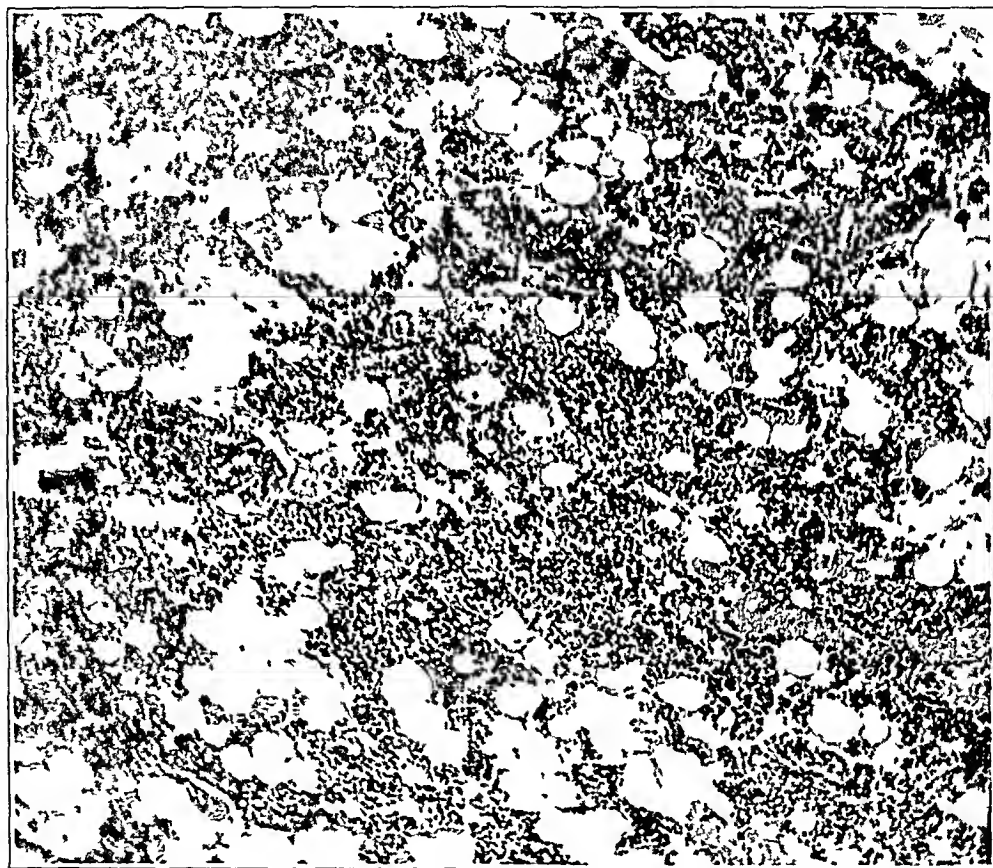


Fig 15—A section through a parathyroid gland showing the marked fatty infiltration.

The testes were small, about the size of an almond. Microscopic examination showed them to be in a preadolescent stage of development, with complete aspermatogenesis (fig 17).

*Pathologic Diagnosis*—The diagnosis was septicemia, infected surgical wound, with diffuse phlegmon of the panniculus and muscle and erysipelatous inflammation of the lower abdominal wall, agonal bacterial embolism in both adrenal glands, massive pulmonary fat embolism, with pulmonary hemorrhage, emphysema and atelectasis, polyglandular dyscrasia (Cushing's syndrome of pituitary basophilism), basophil (?) adenoma of the pituitary body, marked hyperplasia of the thymus gland, hypoplasia of the adrenal glands and aorta, hyperplasia and hypertrophy of the islands of Langerhans, fatty atrophy of the parathyroid glands,

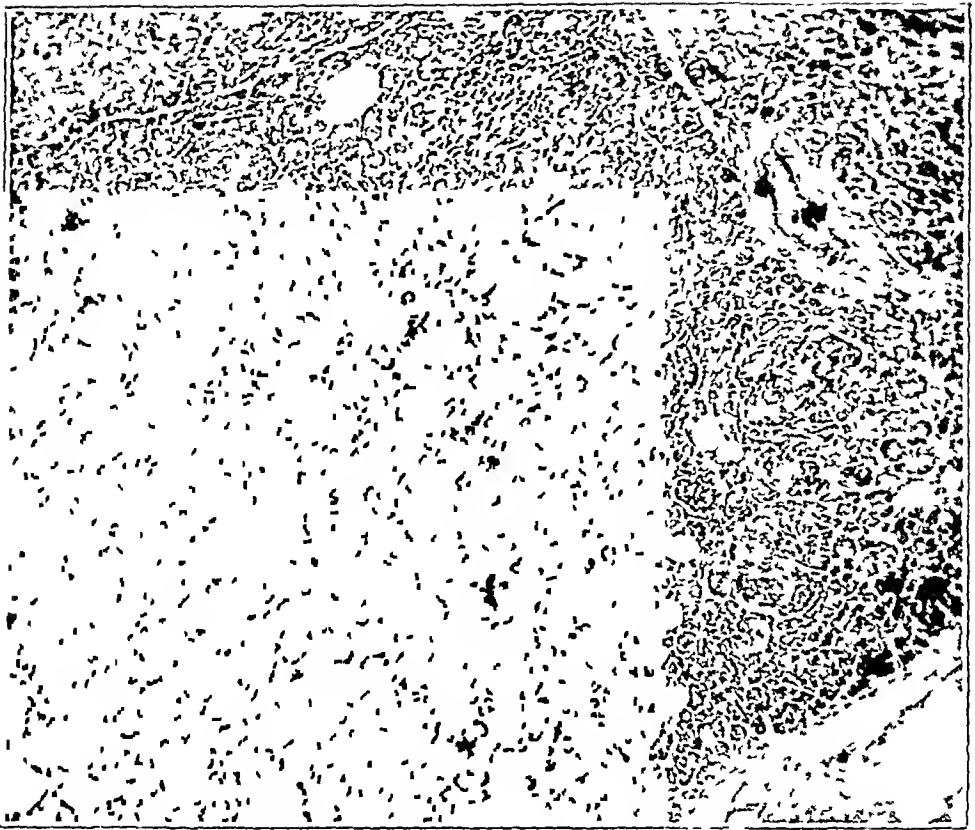


Fig 16—A section of the pancreas, showing the numerous large islands of Langerhans

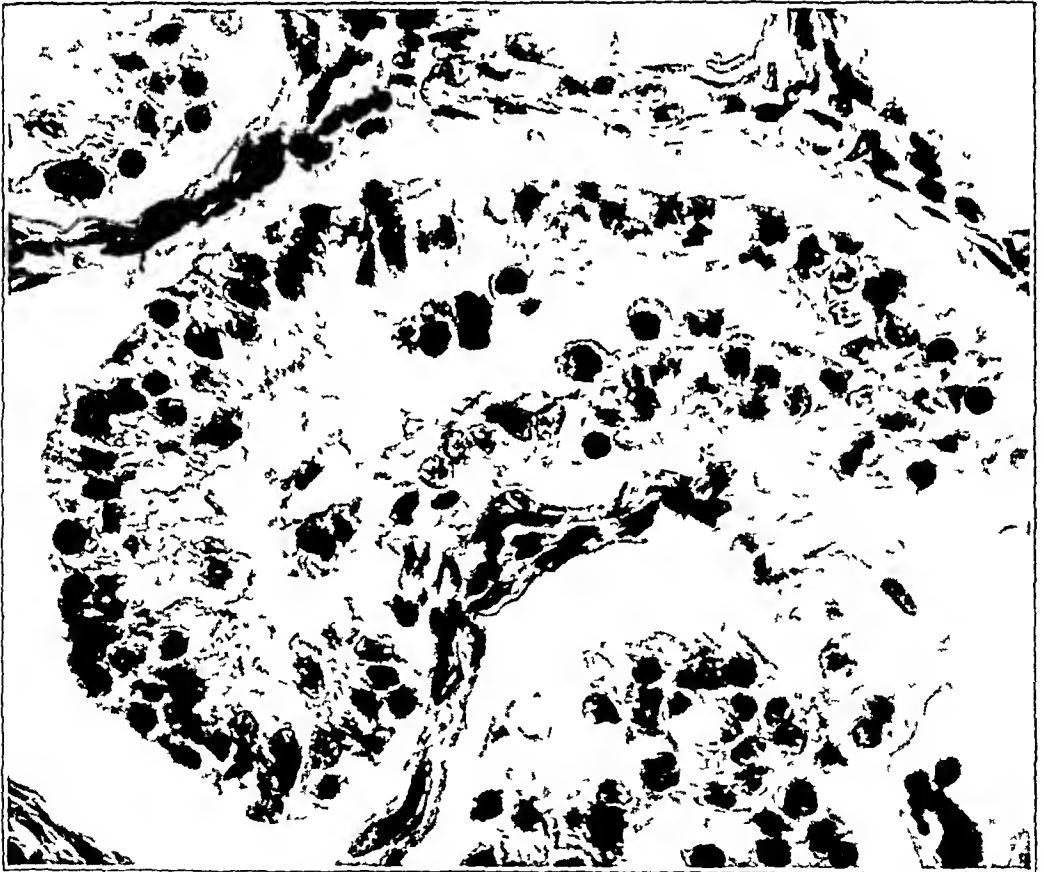


Fig 17—A single seminiferous tubule showing aspermatogenesis. A few aborted attempts at sperm formation are shown in the lumen



hypoplasia of the genitals, aspermatogenesis, lipoidosis of the liver, obesity and generalized osteoporosis, subacute glomerulotubular nephritis, cholelithiasis, moderate hypertrophy of the left ventricle, tuberculosis of the bronchial nodes, acute passive congestion and parenchymatous degeneration of all organs

Chemical analyses of bone obtained at autopsy were made<sup>7</sup> The ash of the femur was found to be 53 per cent, that of the rib, 50 per cent These values are considerably lower than normal The brain tissue (cerebrum and cerebellum) contained 8.6 mg of calcium per hundred grams of tissue The sterol content of portions of cerebrum and cerebellum was 2.34 Gm per hundred grams of tissue

#### COMMENT

There is no doubt that this patient exhibited the features which correspond in detail to those that Cushing described and attributed to basophil adenoma of the hypophysis Most of the reported cases occurred in women Only two of the fourteen verified cases reported by Cushing<sup>8</sup> were in men Of the nine additional verified cases listed in table 1, four were in men Hirsutism, so uniformly a feature of the syndrome in women is not encountered in men. The absence of this feature and of amenorrhea adds to the difficulty of recognition of the syndrome in men

Our patient at no time demonstrated glycosuria Although common, this abnormality is by no means a constant finding in pituitary basophilism The dextrose tolerance test showed a delay in oxidation of dextrose similar to that seen in persons with diabetes

The basal metabolic rate seems to have no characteristic deviation from normal in the reported cases Most commonly it is low, although it ranges from -40 to +42 per cent

Skeletal decalcification has been noted in the majority of cases It has often been slight The extreme generalized demineralization of the skeleton, the "fish spine" and the persistent epiphyseal lines exhibited by our patient are especially striking features

Several of the observations at autopsy on our patient are of unusual interest In the majority of the reported cases the thymus gland was atrophic, in some it was almost completely replaced by fat, in a few it was normal in size The thymus gland in a case reported by Teel<sup>9</sup> weighed 24 Gm and was said to be hyperplastic In our patient, the thymus was huge It weighed 85 Gm and consisted almost entirely of

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7 For the determination of bone ash, small sections of a femur and a rib were dried, extracted with alcohol and ether, again dried and then ashed at a dull red heat in a muffle furnace Total ash was calculated on the moisture-free, fat-free basis

8 Cushing, H "Dyspituitarism" Twenty Years Later, with Special Considerations of the Pituitary Adenomas, Harvey Lectures, 1932-1933, Baltimore, Williams & Wilkins Company, 1934, p 90

9 Teel, H M Basophilic Adenoma of the Hypophysis with Associated Pluriglandular Syndrome Report of a Case, Arch Neurol & Psychiat **26** 593 (Sept) 1931

lymphoid tissue The rôle played by the thymus gland in these cases is apparently not important, since the characteristic features of the syndrome exist no matter what the state of this organ It may very well be, however, that the stormy course which followed operation in our patient was in part resultant from this persistent hyperplastic thymus gland

In most of the verified cases of pituitary basophilism, the adrenal bodies were hyperplastic, some contained adenomas In our case, these glands, although long, were very thin and contained a distinctly hypoplastic cortex (most marked in the glomerular zone) The medulla was also scanty

Cushing<sup>8</sup> suggested that the hypertension associated with this syndrome might be explained on the basis of basophilic activation of the neurohypophysis and that it need not be ascribed to an adrenal source It should be noted that in three of Cushing's group of verified cases and in four of those listed in table 1 (numbers 1, 2, 7 and 8) the adrenal bodies were reported to be normal This lack of recognizable adrenal abnormality in some cases and the occurrence in our patient of adrenal glands with hypoplastic cortices, without adenomas and with scanty medullary tissue, certainly support the contention that the hypertension in these cases is not necessarily due to adrenal changes but may be directly the result of the pituitary lesion

MacMahon, Close and Haas<sup>10</sup> studied the cardiovascular renal changes in two cases of basophil adenoma of the anterior lobe of the pituitary and found that the kidneys showed pathologic changes characteristic of "malignant nephrosclerosis" In our patient the renal damage was not sufficient to cause abnormalities of the urine or any appreciable impairment of renal function Microscopic examination of the kidneys showed a mixture of inflammatory and degenerative changes, and occasional arterioles were sclerosed

#### DIFFERENTIAL DIAGNOSIS

The clinical diagnosis of pituitary basophilism depends on recognition of the syndrome so completely described by Cushing However, cases have been reported in which all the clinical characteristics of "Cushing's syndrome" of pituitary basophilism were present but in which the hypophysis was found to be entirely normal when sectioned serially In these cases lesions were found elsewhere, most commonly in the adrenal glands Frank<sup>11</sup> recently mentioned two cases diagnosed

10 MacMahon, H E, Close, H G, and Haas, G Cardiovascular Renal Changes Associated with Basophil Adenoma of the Anterior Lobe of the Pituitary (Cushing's Syndrome), *Am J Path* **10** 177 (March) 1934

11 Frank, R T A Suggested Test for Functional Cortical Adrenal Tumor, *Proc Soc Exper Biol & Med* **31** 1204 (June) 1934

TABLE 2—Cases of Cortical Adrenal Lesion or Neoplasm of the Thymus

Author	Year Reported	Sex	Age at Onset	Duration of Illness	Clinical Diagnosis	Clinical Findings							
						Obesity	Amenorrhea	Impotence or Sterility	Hirsutism	Cutaneous Striae	Glycosuria	Basal Metabolic Rate	Blood Pressure
Anter, C., McMillan, J. C., Boyd, J., and Cameron, T. Canad. M. A. 25: 188 (Aug.) 1931	1931	F	28	2 yrs	Tumor of adrenal cortex with metastases	+	+		+	+	+		156/120
Smith Pederson, G. Hospitalstid 74: 31 (Dec. 24) 1931	1931	F			Malignant adrenal tumor with metastases	+				+			245/150
Templer <sup>6a</sup>	1933	F	30	2 mos	"Polyglandular dyscrasia"	0	?		+		+	+ 4	Normal
Templer and others <sup>6b</sup>	1934	F	31	1 yr	Adrenal cortical syndrome	Trunk and face	+		+	+	0	-15	168/118
Templer and others <sup>6b</sup>	1934	F	24	1 yr	Adrenal cortical syndrome	Face, neck and trunk	+		+	+	+	+ 1	180/120
Templer and others <sup>6b</sup>	1934	F	4	5 yrs	Adrenal cortical syndrome	Face, neck and trunk	Preocious menses		+	+		-20	172/ 97
Walters and others <sup>6c</sup>	1934	F	38	5 mos	Adrenal cortical syndrome	Face	+		+		0	Normal	170/102
Walters and others <sup>6c</sup>	1934	F	31	5 mos 10 mos 12 mos 14 mos	? ? ? Adrenal cortical syndrome	Face Decreased Increased Increased	0 + +	Slight ?		+	0*		150/100 116/ 76 158/ 96
Templer <sup>6a</sup>	1933	F	45	4 mos	Tumor of adrenal cortex suspected	Face and neck	+		+		+	+20	176/ 80
Escher, F. G., and Cobb-Smith, A. H. T. Proc. Roy. Soc. Med. 7: 404 (Feb.) 1934	1934	F	32	4 yrs	Carcinoma of cortex of left adrenal gland	Face, neck and trunk			+	+	+		205/115
Wright, C. A. M. et al. 141: 191 (Feb.) 1935 (case 4)	1935	F	22	18 mos	Carcinoma of adrenal cortex	Face, neck and trunk			+	+		+ 4	156/120
Keyton, O., Turnbull, H. M., and Patton, A. B. Path. & Bact. 34: 35 (Sept.) 1931	1931	M	30	1 yr	No diagnosis made	Face and abdomen		+		+	+		170/100
Keyton, O. Lancet 1: 1221 (June) 1934	1934	M	11	3 mos	Disease of pituitary gland or of adrenal glands	Face and abdomen		+		0	+		125/ 85
Brown, W. H. Lancet 2: 1022 (Nov. 17) 1928	1928	F	45		Pluriglandular defect	Generalized					+	+20	240/160

## *Gland Showing Many or All of the Characteristics of Pituitary Basophilism*

Pathologic Condition	Comment
Tumor of right adrenal gland larger than 1 fetal head	No autopsy, diagnosis of tumor of adrenal made from pathologic examination of metastases
Pituitary gland said to be normal, not examined microscopically, malignant neoplasm of adrenal gland 12 by 6 cm	
Thyroid gland not examined, thymus gland not examined, carcinoma of entire head of pancreas, metastases in liver, carcinoma of left adrenal gland (operation)	Physiologic characteristics not typical of Cushing's syndrome, reaction to Friedman test +
Pituitary gland normal (serially sectioned), thyroid gland atrophic, fatty, combined weight of adrenal glands 35 Gm both enlarged, normal histologic picture except for two small adenomas in left cortex, gonads small, sclerotic, with small cysts	
Adenoma of cortex of right adrenal glands, 10 by 12 cm, 600 Gm (operation)	Six months postoperative, felt well, appeared to illness, obesity and hirsutism gone, blood pressure normal
Right adrenal gland half normal size, left, tumor 6 by 4 by 2 cm, cortical adenoma (operation)	After operation, lost 31 pounds (14 Kg), ceased, hirsuties disappeared, basal metabolic -9 blood pressure 98/62
Right adrenal gland normal left, 2.7 by 2 by 5 cm adenocarcinoma, weight 5.4 Gm (operation)	Two months postoperative, face normal, blood pressure 130/76, stronger
Marked enlargement of adrenal glands, cortical hyperplasia, no adenoma (operation, part of each gland removed)	Four months postoperative, face less swollen, unrestricted and no glycosuria
Pituitary gland normal (serial sections made), tumor of thymus "thymoma," 5 cm in diameter, adrenal glands very large, combined weight 49 Gm, ribs friable and could be broken easily with fingers	Friedman reaction negative, serum proteins, per hundred cubic centimeters
Pituitary gland showed increase in basophil cells, one collection 0.3 mm in diameter, carcinoma of cortex of left adrenal gland, right normal gonads atrophic, osteoporosis "extreme" +++, death after adrenalectomy	Authors consider it "doubtful" if the collection of basophil cells in hypophysis could be due to an adenoma
Carcinoma of cortex of right adrenal gland, weighing 1,350 Gm, death 24 hours after removal of carcinoma of adrenal cortex	Author expressed the belief that pituitary basophilism might have been associated with the cause of the tumor of the adrenal; autopsy not permitted
Pituitary gland normal (serially sectioned), hypertrophy of thyroid gland, parathyroid bodies normal, oat cell carcinoma of thymus gland 6.2 by 4.8 by 2.5 cm, pancreas "not definitely abnormal" adrenal glands enlarged, combined weight 44.3 Gm, practically no medulla, all cortex, active spermatogenesis, combined weight of gonads 27.9 Gm, no osteoporosis, death caused by respiratory obstruction (cellulitis of neck)	
Pituitary gland normal (not examined by serial sections), thyroid gland hyperplastic, oat cell carcinoma of thymus gland 3.7 by 3 by 1.5 cm, pancreas normal, enlargement of adrenal glands, especially of cortex, combined weight 20.6 Gm, normal histology, death from hypoglycemia (?)	
Pituitary gland enlarged, much colloid, no mention of serial sections, adenomatous hyperplasia of thyroid gland, colloid present, thymus gland replaced by fat, pancreas normal, adrenal glands hypertrophic, patch of perivascular lymphocytic infiltration in medulla, gonads enlarged, fibrotic, death caused by heart failure and nephritis	Oat cell carcinoma 1 cm in diameter found in thymus gland in cases 12 and 13 with histologic picture exactly like that found in thymus gland in cases 12 and 13

\* Diet restricted in carbohydrate

Author	Sex	Age at Onset	Duration of Illness, Years	Clinical Observations Prior to Roentgen Therapy							Roentgen Therapy to Hypophysis									
				Obesity	Amenorrhea	Impotence	Hirsutism	Striae	Glycosuria	Basal Metabolic Rate	Blood Pressure	Skeletal Decalcification	Interval Between Treatments, Months	Factors of Treatment						
														Kilovolts	Milliamperes	Copper, Thickness, Mm	Filter Aluminum, Thickness Mm	Focal Skin Distance, Cm	Time Minutes	Ports
Cases ung <sup>s</sup> (S P)	F	20	13	Face	+		++	++		-40 -1	240	Atrophy of vertebrae, fractures spine, skull, pelvis Skull		185		1/2	1	40 to 46		2 4 1,200
er <sup>ea</sup>	F	30	5	Neck, trunk abdomen	+		+	+	+	-10 -20	160/120			200	5	3/4	1	50	60	3* 3 1,400
burg, Arb a urol a d a Univ 143, 1933 g, J, Cran, Quart ed 3 an) 1934 ght, M 141: Feb 20)	M	23		Face, abdomen	+			+	+	-28	Elevated		1	200 †	5	3/4	1	50	60	3* 3 1,400
	F	24	4	Abdomen, thighs, upper part of arms	+		+	+	0		180/118	+		†						
	M	10	1 1/2	Face, neck, trunk				+	0	-18	154/110	Thin vertebrae	2	210 210	5 5	1 1		50 50	240 240	2 16 3,000 2 18 3,000
berg others	M	12	7	Face, neck, trunk		+	0	+	0	-3 -12 -24	155/125	+++		200	30	1/2	1	50	33	2 5 1,600
Diagnoses Patients Living when Case was Reported	M	25	7	Abdomen		+	Loss of hair	+	+	+10 -1 -10	165/ 70 178/100	0		185		1/2	1	40		2 4 700
ung <sup>s</sup> (e D)	F	8	7	Face, neck, trunk	+		+	+	+	-28 -33 -22	140/110 180/110	Marked		185 1 1/2 185 2 185 3 185 4 185 8 185 2 185 2 185		1/2 1/2 1/2 1/2 1/2 1/2 1/2	1 1 1 1 1 1 1	40 to 46 Same Same Same Same Same Same Same		2 6 1,000 2 5 1,000 2 4 1,300 2 4 1,120 2 4 1,200 2 4 1,200 2 4 1,200 2 4 1,200 2 4 1,200
er <sup>ea</sup>	F	23	4	Abdomen	0		+	+		-9	Elevated	Marked		200	5	3/4	1	50	60	4 4 1,000
lee, Arch ol & hiat 1007 7) 1934 1 2	F	16	14	Abdomen	0		+	+		-15	150/110	Skull		†						
	F	23	1	General	+		+	+	0	-7	Normal	Atrophic vertebrae		†						
3, C Roy Med 395 1) 1934 hard, B Roy Med 673 11) 1934 rence, Proc Soc 27 275 1) 1934	F	37?		General	+		+	+	0	+ 5	170/ 90 160/110 185/125	0 0 0		† † †						
	F	26	14	+	0		+		0		190			†						
	F	33	4	+	+		+				160/110 170/125	+	3	180 180		1/2 1/2	1 1	45 45		2 25 3,800 2 24 1,700
In, F eben Wehnschr 1045 (July 1085 (July 934 ht, M 141: 191 20) 1935 2	M	13	1	+			+	+	+	-10	125/ 85 210/130	Marked "fish spine"		200	6	1/2		46		3 4 1,400
ht, M 141: 191 20) 1935 2	F	?	?	+	\$	\$	+	+		-8	180/125 200/128	Marked spine and skull	2	210 210	5 5	3/4 3/4	1 1	240 240		2 16 3,000 2 31 3,000
I, M G, re, J R. Young, R ology 53 (Jan )	F	20	3	+ 232 pounds (105 kg)	†		Slight	+	0	-26	140/ 85 155/ 90	Areas of rarefaction in tibia metatarsals and phalanges		160 av 218 pk		1/2	1	50		2 49 1,500

Roentgen therapy given to the thymic region also  
 Factors of treatment not known  
 nearly as could be calculated from the factors known

\$ Scanty menses  
 # Frigid  
 † Scanty irregular menses

Interval After Roentgen Therapy	Clinical Observations After Roentgen Therapy	Comment
1 mo		"No immediate effects of any appreciable kind," 1 month after treatment (acute pulmonary ed
1 mo		"No material change," adrenal glands normal at of surgical exploration
10 mo (approximately) 3 yr		No knowledge of change, death within 1 year first roentgen therapy was given
4 mo		No knowledge of change, death 3 years after ro therapy
5 mo 3 mo	Blood pressure, 160/132	No mention made of any improvement, death 4 after therapy (purulent bronchitis and emphysema)
6 mo	No change in obesity, impotence persisted, no hirsutism striae, the same as before, no glycosuria, blood pressure 160/130 and 175/135, no change in skeletal decalcification	"Definite improvement, patient felt better and no headaches, no backache except on motion, plethora" death 3 months after last tre laparotomy)
1 yr	Glycosuria disappeared, patient on general diet at time of last report	No change was noted after roentgen therapy, 6 months after therapy following exploratory tion of left adrenal gland
4 mo 2½ mo	Apparent diminution of hirsutism, increasing striae, continued to gain weight	"Almost immediate striking improvement in strength and resistance to infection", (Dr Woodyatt that he was "skeptical of influence of radioactivity in this case") Became alert and interested in life, far better had been for a long time, improvement chiefly of well being, less plethora
1 yr 4 mo	Obesity disappeared, normal menses were present, hirsutism disappeared, blood pressure became normal	"Is enjoying excellent health"
1 yr ? 1+ yr 1½ yr	Return of menses	"No material change so far as I have been able to learn" (adrenal glands appeared normal at surgical exploration)
2 yr	Obesity disappeared except on face, amenorrhea persisted no change in hirsutism, striae were more marked, no glycosuria, blood pressure 170/115, no skeletal decalcification	"Less fatigue and infection"
7 mo 4 mo	Obesity less, most on shoulders and chest, amenorrhea since roentgen therapy, hirsutism increased, ++ no glycosuria, blood pressure same, large bones showed rarefaction	No other change Improvement of headaches Besides roentgen therapy the patient received treatment by extract and strict diet
2 mo 8 mo	Obesity disappeared, menses began hirsutism less, only occasional trace of glycosuria, blood pressure 124/85, skeletal decalcification improved	Disappearance of polyuria since roentgen therapy laparotomy 2 years prior to therapy revealed right adrenal gland and pelvic organs
7 mo 4½ mo	Obesity disappeared, striae became paler, blood pressure 105/65 and 110/70	Disappearance of leg pains, bruising, thirst, hunger, slight exophthalmos, retinal hemorrhages and less, general weakness unchanged, diet of 100 Gm carbohydrate needed 40 units of insulin before therapy, after therapy 150 Gm carbohydrate satisfactory without insulin
2 mo 8 mo	Obesity absent, no hirsutism, striae pale and atrophic, no glycosuria, basal metabolic rate, +16, blood pressure 110/75 and 125/85, much improvement in skeletal decalcification	Great improvement in strength, prior to therapy not stand alone, after therapy could climb stairs Felt entirely well at time of report, kyphosis recognizable remnant of previous syndrome, activity and growth
7 mo 4½ mo	Libido returned, hirsutism less, blood pressure 220/160, marked increase in density of spine	"Much improved, less plethora, headaches less weakness persists, ecchymoses occur"
2 mo	Obesity reduced, blood pressure decreased, areas of rarefaction smaller, new bone formed	"General condition promptly improved", leg decreased
11 mo	Weight reduced to 187 pounds (80.8 Kg), normal menses, blood pressure 140/90, scarcely any defects in the bones	Patient received a 1,500 calory diet and desiccated thyroid, 1 grain three times a day, therefore, difficult to evaluate results of roentgen therapy

clinically as examples of pituitary basophilism, in both the pituitary gland (serial sections in one case) was found to be normal, and in each a carcinoma of cortical adrenal origin was found. Kepler<sup>6</sup> and Walters<sup>12</sup> reported a series of cases in which there were clinical manifestations similar to Cushing's syndrome and the patient was apparently cured by surgical removal of a cortical suprarenal adenoma or of portions of hyperplastic adrenal glands.

In table 2 are listed the salient features of all reported cases which have come to our attention in which the condition clinically simulated pituitary basophilism, and in which lesions considered to be the cause of the syndrome have been found elsewhere than in the hypophysis. Only those cases in which there was histologic verification have been included. In the first eleven cases the causative lesion was ascribed to a neoplasm or to atrophy of the adrenal glands. In cases 12 and 13 the malady was ascribed to an oat cell carcinoma of the thymus. (A thymoma also occurred in case 9). In the fourteenth case, besides the hypertrophic adrenal glands, an oat cell carcinoma was found in the lungs. In cases 4, 9 and 12 the pituitary gland was examined by serial section and found to be normal. In the cases in which the patient was not examined post mortem it is possible, of course, that pituitary lesions may have existed. Cases 5, 6, 7 and 8, in patients who were living when the cases were reported, were included in the group because of the proof of adrenal abnormality by examination of material obtained at surgical operation and especially because of the improvement following the removal of an adrenal neoplasm or of part of a hyperplastic adrenal gland.

It should be noted that although the significant lesion in some cases was thought to be a neoplasm of the thymus gland, in all these cases adrenal hypertrophy, especially of the cortex, existed.

It is seen, then, that there are on record cases of "multiglandular disease" exhibiting similar clinical syndromes, in some of which the pituitary gland was proved to be normal at postmortem examination, and a lesion was found in the adrenal glands. Other cases have been reported in which there were normal adrenal glands and proved hypophyseal basophilism. The difficulty of making a correct clinical diagnosis in some cases is evident. Roentgenograms of the sella turcica are of no help in differentiating these conditions for the pituitary lesion, when it exists is usually so small that changes of the bones are not produced. When no direct indication of adrenal lesion is present (palpable tumor or distorted pyelograms), one has no means of definitely locating the lesion responsible for the syndrome.

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12 Walters W, Wilder R M, and Kepler E J. Progress Subsequent to Subtotal Bilateral Suprarenalectomy for the Suprarenal Cortical Syndrome, Proc Staff Meet Mayo Clin 9:661 (Oct 31) 1934. Walters and others<sup>6c</sup>

It seems wise in cases in which the causative lesion cannot be definitely learned to treat the patient for pituitary basophilism and to administer roentgen therapy to the pituitary gland. If no benefit results, certainly the adrenal glands should be exploited, and any abnormality found should be treated as the conditions indicate. This plan of treatment seems most wise, especially since patients with pituitary basophilism are peculiarly susceptible to infection and are therefore poor surgical risks.

#### ROENTGEN THERAPY IN CASES OF PITUITARY BASOPHILISM

Data on all the known cases of pituitary basophilism in which roentgen therapy has been applied to the hypophysis are tabulated in table 3. The original clinical findings, the details of therapy and the results obtained are noted.

Wright's case (5) is the only one in which the diagnosis of basophilism has been verified in which the condition was reported to be improved after roentgen therapy. The improvement in this patient was chiefly in the state of general well-being. The blood pressure was higher after treatment than before. Changes in many of the cardinal features of the disease are not mentioned.

Of the unverified cases, the condition in that of Kepler (case 9) and in that of Pritchard (case 14) was not improved by roentgen therapy. Improvement in only one symptom was reported for each of Pardee's patients (cases 10, 11 and 12), and certainly no dramatic results were reported in any of his cases. In Wall's patient (case 13), obesity disappeared, but the strict diet and thyroid medication could very well account for this improvement. Wohl's patient (case 18) showed reduction in weight, return of regular menses and an improved skeleton, but in this patient too the reduction diet and thyroid medication make it difficult to evaluate roentgen therapy. In the remainder of the cases the condition was reported as improved.

In some cases the improvement was marked. A most gratifying result from roentgen therapy was noted in the case reported by Jamin (case 16). A boy aged 14 showed a rapid development of Cushing's syndrome and a rapid return to normal following roentgen therapy directed to the hypophysis. Within two months his appearance was again almost normal, the blood pressure returned to normal and his strength improved, so that he could walk about and climb stairs (previous to therapy he could not stand alone). Within eight months he was able to ride long distances on a bicycle and to enter into all activities with his companions.

Almost as dramatic is the case of Alice D. (case 8), one of Cushing's patients. She did not improve as rapidly as did Jamin's patient, however, persistence in treatment was rewarded by a return to normal.



appearance and disappearance of hypertension Cushing<sup>13</sup> reported this patient to be in "excellent health" at the time of this writing (one year after the last roentgen treatment)

Table 3 lists instances in which roentgen therapy as given was of no value and others in which apparent cure was effected This wide variation in results is interesting and might be explained by the combined effect of several contributing factors It is most likely that different basophil adenomas vary in their sensitivity to the roentgen rays Jamín's patient, for instance, who showed marked and rapid improvement, received practically the same dose of roentgen therapy, given with similar factors, as did our patient, who showed no sign of improvement in six months The age of the patient may be a factor, but it does not seem to be of major importance The two patients showing the greatest improvement were only 14 and 15 years of age, but Lawrence's patient (case 15) was 37 years of age It may be that the duration of illness before roentgen therapy is instituted is a factor The patients exhibiting recognizable features of Cushing's disease for 13 or 14 years (cases 1 and 14) were not benefited by roentgen therapy

The method of administering roentgen therapy and the amount of irradiation appear to be especially important factors and should receive careful consideration In every case listed in table 3 in which large amounts of roentgen rays were applied to the hypophysis the condition was markedly improved The patient in case 8 was given repeated treatments, each of moderate size In cases 5, 15 and 17 more intensive and fewer treatments were given with good results The failure of roentgen therapy in our case and in other reported cases might very well be explained by the fact that this treatment was not sufficiently pursued or that the dosage was insufficient It would seem that much can be done for these patients if roentgen therapy in sufficient doses is persistently applied

#### SUMMARY

A verified case of pituitary basophilism showing the classic clinical syndrome has been reported

The essential features of other verified cases reported since Cushing's review (1933) have been summarized

The resemblance of the clinical manifestations of other lesions, especially cortical adrenal neoplasm or hyperplasia, to "Cushing's syndrome" of pituitary basophilism has been pointed out

The results of roentgen therapy directed to the hypophysis in cases of Cushing's disease have been reviewed This study indicates that roentgen therapy should be intensively and persistently pursued in cases of pituitary basophilism

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13 Cushing, H    Personal communication to the authors

# CALCIUM AND PHOSPHORUS METABOLISM IN A VERIFIED CASE OF PITUITARY BASOPHILISM

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AND

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Patients with pituitary basophilism commonly have generalized demineralization of the skeleton. In some cases this is so severe that multiple fractures occur. The cause of this skeletal abnormality has been obscure. Cushing<sup>1</sup> suggested that the parathyroid bodies might be activated to excessive secretion by the pituitary lesion and thus cause the osteoporosis.

In the majority of verified cases of pituitary basophilism the parathyroid glands when examined post mortem are described as being normal, fatty or atrophic. In several cases the parathyroid glands were enlarged but were found to be grossly infiltrated with fat, which contributed to their size. In only one case has a parathyroid adenoma been found.<sup>2</sup> Only in the case described in 1912 by Schmorl<sup>3</sup> and later by Molineus<sup>4</sup> has hyperplasia of the parathyroid glands been observed. The patient exhibited the clinical syndrome of pituitary basophilism and at postmortem examination was found to have a large basophil adenoma of the hypophysis, oxyphilic hyperplasia of the parathyroid bodies without adenomatous formation and "brown tumors" of the bone. The relationship of the pituitary and parathyroid lesions in this case is not clear.

In the present state of our knowledge, it is hazardous to interpret the functional behavior of the parathyroid glands from their histologic appearance. It would seem, therefore, that a study of the calcium and

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The expense of this investigation was defrayed in part by Parke, Davis & Co.

From the Department of Internal Medicine, Medical School, University of Michigan.

1 Cushing, H. "Dyspituitarism" Twenty Years Later, with Special Considerations of the Pituitary Adenomas, Harvey Lectures, 1932-1933, Baltimore, Williams & Wilkins Company, 1934, p. 90.

2 Since these data were compiled, a case of verified pituitary basophilism has been reported by J. A. Lawrence and H. M. Zimmerman (Pituitary Basophilism Report of a Case, Arch Int Med **55** 745 [May] 1935), in which one parathyroid body contained an adenoma.

3 Schmorl, G. Gesellschaft für Natur und Heilkunde zur Dresden, offizielles Protokoll, München med Wchnschr **59** 2887, 1912.

4 Molineus. Ueber die multiplen braunen Tumoren bei Osteomalacie, Arch f klin Chir **101** 333, 1913.

phosphorus metabolism would be a more reliable approach to an understanding of the fundamental disturbance responsible for the skeletal changes. Such studies of the mineral metabolism in pituitary basophilism have been very meager. Aub studied two of Cushing's<sup>5</sup> cases, but only while the patients had a low intake of calcium. In one case there was normal elimination of both calcium and phosphorus, in the other there was increased excretion of calcium in the urine. The urinary phosphorus, however, was not increased. The only other studies of mineral metabolism reported are those of Wall,<sup>6</sup> who observed the calcium and phosphorus exchange over a period of six days in an unverified case of pituitary basophilism, while the intake of calcium was low.<sup>7</sup> Several investigators have reported the calcium and phosphorus concentration of the serum in cases of Cushing's disease. The results of all these studies of calcium and phosphorus metabolism are presented in table 1.

The purpose of this communication is to report studies of the calcium and phosphorus metabolism made over a long period in a verified case of pituitary basophilism. A complete account of the clinical and pathologic findings in this case have been reported elsewhere.<sup>8</sup> Roentgenograms of this patient Z. K. demonstrated an extreme degree of generalized skeletal demineralization without the formation of cysts, a typical "fish spine" fragmentation of the heads of the femurs and metatarsal bones and nonunion of many epiphyses.

The mineral metabolism was studied for three months. The patient then received roentgen therapy to the pituitary gland, and, after an interval of two months, the calcium and phosphorus exchange was again observed for a period of eleven weeks.

#### OBSERVATIONS ON THE PATIENT

*Method*—Studies of the calcium, phosphorus and nitrogen balance were carried out while the patient was receiving diets of different calcium and phosphorus content and while he was receiving various supplements. One and five-tenths liters of distilled water were given daily. The ingesta and all excreta were quantitatively analyzed for calcium, phosphorus and nitrogen, and the exchange was calculated on

5 Cushing H. Further Notes on Pituitary Basophilism, *J. A. M. A.* **99** 281 (July 23) 1932. Cushing<sup>1</sup>

6 Wall, C. Adreno-Genital Syndrome (Cushing Type), *Proc. Roy. Soc. Med.* **27** 395 (Feb.) 1934.

7 The calcium metabolism was studied in the case recently reported by Lawrence and Zimmerman<sup>2</sup> and found not to show the usual picture of hyperparathyroidism.

8 Freyberg R. H., Barker P. S., Newburgh L. H., and Coller, F. A. Pituitary Basophilism (Cushing's Syndrome). Report of a Verified Case, with a Discussion of the Differential Diagnosis and Treatment. *Arch. Int. Med.*, this issue, p. 187.

TABLE 1—Calcium and Phosphorus Data on Cases of Pituitary Basophilism Taken from Literature

Author	Clinical Diagnosis	Pathologic Diagnosis	Osteoporosis	Serum		Calcium Exchange (3 Day Periods)				Phosphorus Exchange (3 Day Periods)			
				Cal Mg per 100Cc	Phos phorus, Mg per 100Cc	Intake, Gm	Urine, Gm	Feces, Gm	Total Excre- tion, Gm	Intake, Gm	Urine, Gm	Feces, Gm	Total Excre- tion, Gm
Cushing <sup>1</sup> (Miss P)	Pituitary basophilism	Basophilic adenoma of adenohypophysis	Slight	Nor mal	Nor mal	I 0.30 II 0.30 Av 0.30	0.65 0.84 0.74	0.27 0.48 0.37	1.86 1.86 1.86	0.87 0.75 0.81	0.47 1.08 0.77	1.34 1.83 1.58	0.52 0.03 0.25
Cushing <sup>2</sup> (Alice D)	Pituitary basophilism	Living at time of report	++	9.8	2.7								
Wall <sup>3</sup>	Adrenogenital syndrome (Cushing type)	Living at time of report	None	10.4	2.8	I 0.31 II 0.31 Av 0.31	0.42 0.55 0.48	0.79 0.61 0.70					
Crang, J. and Cran, B. S. Quart J Med 3: 57 (Jan) 1934	Basophilic adenoma of pituitary	Basophilic ade- noma of anterior lobe of pitui- tary body	+	10.8	2.01								
Wright, C. A. M Rec 141: 191 (Feb 20) 1935	Pituitary basophilism	Basophilic pituitary adenoma	Thin vertebrae	9.8	9.0								
Buttshauser, E. Deutsches Arch f Klin Med 175 640, 1933	Osteoporotic obesity	Increase in basophils with adenoma like hyperplasia	++	10.0	2.5								
Kepler, E. J. Proc Staff Meet., Mayo Clin 8: 102 (Feb 15) 1933	Polyglandular dyscrasia	Normal adrenal glands at opera- tion, living at time of report	Skull, spine ribs, multiple fractures	9.6	2.64	11.4							
Lawrence, R. D. Proc Roy Soc Med 27: 275 (Jan) 1934	Cushing's pituitary basophilism	Living at time of report	+ Fractured ribs and os pubis	9.7	2.0	0.506							
Wohl, M. G., Moore, J. R., and Young, B. R. Radiology 24: 53 (Jan) 1935	Basophilic adenoma	Living at time of report, im- proved by roent- gen therapy to pituitary	None of spine and ribs, areas of rarefaction in metatarsal bones, phalanges and right tibia	11.5	4.0								

the basis of three day metabolism periods. Whenever the nitrogen balance was negative, the intake of calcium and phosphorus was corrected by the amount of these elements liberated by the destruction of tissue. At frequent intervals determinations of serum calcium and phosphorus were made.<sup>9</sup>

*First Study*—Results of the study are presented in table 2. In figures 1 and 2 the calcium and phosphorus exchange and the concentration of these elements in the serum are plotted for the first forty three day periods.

Throughout this first metabolism study, the diet was made undernourishing (890 calories) in order to reduce the patient's weight. The calcium content of

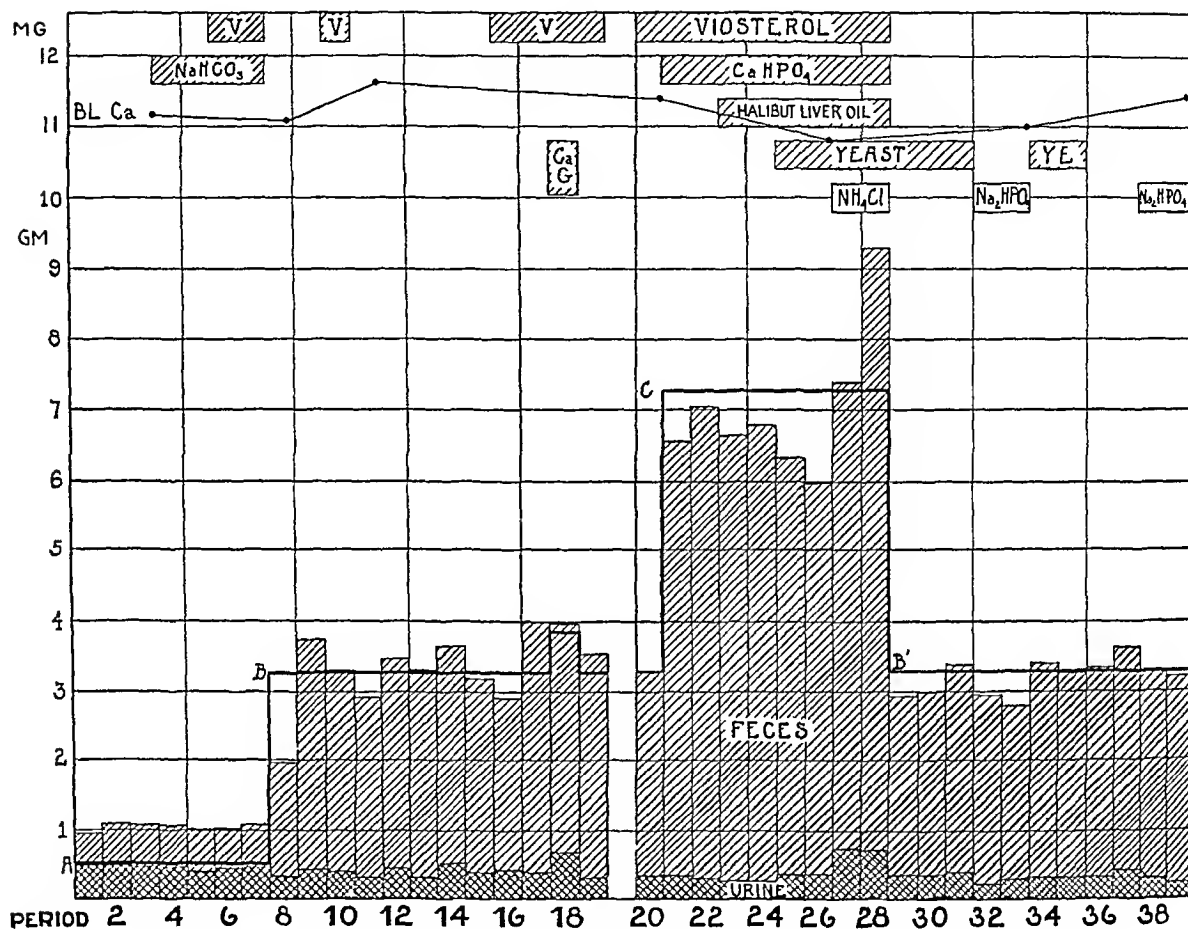


Fig 1—Calcium exchange and concentration of calcium in the serum during the first metabolism study of Z K. The heavy line represents the total intake, and each column represents the excretion of calcium during one period (three days).

<sup>9</sup> Chemical methods employed. Calcium in the urine was determined by the method of Shohl and Pedley (J Biol Chem 50 537, 1922) and in the feces and diets by the Tisdall-Kramer procedure (J Biol Chem 48 1, 1921). For the estimation of serum calcium, the Clark-Collip (J Biol Chem 63 461, 1925) modification of the Tisdall method was used. The methods of Fiske and Subbarow (J Biol Chem 66 375, 1925) were employed for all phosphorus determinations. All nitrogen analyses were made by the Kjeldahl method. Titratable acidity of the urine was measured by the method of Henderson and Palmer (J Biol Chem 17 305, 1914). Urinary ammonia was determined by the Folin-Bell (J Biol Chem 29 329, 1917) method.

TABLE 2—First Study of Calcium and Phosphorus Metabolism in Patient Z K

Diet	Period	Medication	Nitrogen			Total Urinary Acid*			Calcium			Phosphorus		
			Intake, Gm	Output, Gm	Balance, Gm	Ce N/10	Intake, Gm	Urine, Gm	Feces, Gm	Total Excretion, Gm	Balance, Gm	Intake, Gm	Urine, Gm	Total Excretion, Gm
Low calcium, 890 calories, calcium phosphorus ratio 0.46	1		15.1	13.67	1.43	1,546	0.49	0.47	0.48	0.94	-0.45	1.06	Lost	1.06
	2		15.1	17.86	-2.76	1,421	0.50	0.47	0.62	1.09	-0.59	1.22	0.62	1.90
	3		15.1	17.32	-2.22	1,308	0.50	0.45	0.63	1.08	-0.58	1.19	0.52	1.74
	4	Sodium bicarbonate 3.84 Gm	15.1	17.31	-2.24	830	0.50	0.44	0.61	1.05	-0.55	1.19	0.60	1.68
	5	Sodium bicarbonate 11.52 Gm	15.1	16.20	-1.1	209	0.49	0.39	0.61	1.0	-0.50	1.12	0.94	1.61
	6	Sodium bicarbonate 17.28 Gm, viosterol †	15.1	14.72	0.38	360	0.49	0.42	0.60	1.02	-0.53	1.06	0.67	1.61
High calcium diet, 890 calories, calcium-phosphorus ratio 1.31	7	Sodium bicarbonate 17.52 Gm, viosterol †	15.1	17.17	-2.08	189	0.50	0.44	0.62	1.06	-0.56	1.17	0.70	1.77
	8		16.95	17.07	-0.12	474	3.26	0.54	1.60	1.94	1.32	2.50	1.07	2.21
	9		16.95	18.35	-1.4	897	3.28	0.41	3.30	3.71	-0.43	2.57	1.21	3.15
	10	Viosterol †	16.95	19.87	-2.92	1,018	3.28	0.38	3.27	3.27	-0.01	2.66	1.61	3.30
	11		16.95	19.47	-2.52	1,161	3.28	0.32	3.57	2.89	0.30	2.66	1.09	1.54
	12		16.95	20.86	-3.91	1,024	3.28	0.42	3.00	3.42	-0.13	2.71	1.20	1.65
	13		16.95	20.87	-3.92	1,089	3.28	0.32	2.99	3.31	-0.02	2.71	1.32	1.59
	14		16.95	20.82	-3.87	1,094	3.28	0.48	3.13	3.61	-0.32	2.71	1.28	1.78
	15	Viosterol †	16.95	20.12	-3.17	1,106	3.28	0.38	2.92	3.18	0.10	2.67	1.19	1.31
	16	Viosterol †	16.95	19.64	-2.69	1,270	3.28	0.40	2.47	2.87	0.41	2.64	1.10	1.60
Intravenous injection of calcium gluconate (0.54 Gm calcium)	17	Viosterol †	16.95	19.94	-2.99	833	3.30	0.37	3.61	3.98	-0.68	2.66	1.02	2.16
	18		16.95	20.50	-3.55	1,026	3.84	0.67	3.28	3.95	-0.11	2.69	1.07	1.66
	19		16.95	19.36	-2.41	921	3.30	0.28	3.21	3.49	-0.19	2.63	1.07	1.79
	20		16.95	17.43	-0.48	789	3.28	0.34	2.92	3.26	0.02	2.52	0.95	1.76
	21		17.45	16.98	0.47	1,764	7.24	0.34	6.23	6.56	0.08	5.28	1.27	3.66
	22		17.45	19.11	-1.66	1,210	7.24	0.28	6.74	7.02	0.22	5.38	1.32	4.10
	23		17.68	19.1	-1.42	1,218	7.24	0.25	6.36	6.61	0.63	5.36	1.25	3.51
	24		19.98	18.62	-0.91	1,248	7.24	0.23	6.53	6.76	0.48	5.34	1.36	3.30
	25	9 cakes compressed yeast	19.98	20.31	-0.33	1,247	7.24	0.36	5.93	6.29	0.95	5.08	1.31	3.75
	26	9 cakes compressed yeast	19.98	21.77	-1.79	1,085	7.24	0.36	5.60	5.96	1.23	5.76	1.55	2.61
Halibut liver oil 14 Gm CaHPO <sub>4</sub> 18 Gm ammonium chloride	27	9 cakes compressed yeast and 18 Gm ammonium chloride	25.51	22.92	2.59	2,727	7.24	0.73	6.65	7.38	-0.14	5.66	1.85	3.01
	28		25.51	30.09	-4.58	3,453	7.25	0.71	8.52	9.23	-1.98	5.92	1.85	4.59
	29	9 cakes compressed yeast	19.25	23.86	-4.61	2,463	3.29	0.35	2.55	2.90	0.39	3.14	1.17	1.50
	30	9 cakes compressed yeast	19.25	21.35	-2.1	1,373	3.28	0.35	2.64	2.99	0.29	2.99	1.0	1.60
	31	9 cakes compressed yeast	19.25	20.11	-0.86	1,013	3.28	0.33	2.93	3.36	-0.29	2.92	1.04	1.66
	32	2 Gm di sodium hydrogen phosphate	17.1	16.94	0.16	928	3.28	0.21	2.72	2.93	0.35	2.86	1.09	1.27
	33	2 Gm di sodium hydrogen phosphate	17.1	16.42	0.66	817	3.28	0.27	2.49	2.76	0.52	2.86	1.20	1.25
	34	Yeast extract	17.35	17.73	-0.38	857	3.28	0.28	3.10	3.38	-0.10	2.61	0.95	1.78
	35	Yeast extract	17.35	17.64	-0.31	917	3.28	0.29	2.95	3.24	-0.04	2.60	1.06	1.24
	36		16.95	17.96	-1.01	999	3.28	0.32	2.98	3.30	-0.02	2.55	1.03	1.65
10.8 Gm di sodium hydrogen phosphate 10.2 Gm di sodium hydrogen phosphate	37		16.95	17.83	-0.88	1,069	3.28	0.40	3.18	3.58	-0.30	2.54	0.99	1.75
	38		17.29	17.54	-0.25	954	3.28	0.28	2.96	3.26	0.02	2.40	1.00	1.90
	39		17.4	17.79	-0.39	845	3.28	0.22	2.96	3.18	0.10	4.01	1.72	1.46
	40		16.95	17.23	-0.28	933	3.28	0.22	3.08	3.25	0.03	2.51	0.86	1.74

\* Urine iv ammonia plus titratable acidity

† 1.2 Gm of viosterol supplying 94,000 U S P XI units of vitamin D per period

‡ 3.6 Gm halibut liver oil supplemented by viosterol, supplying 16,128,000 U S P XI units of vitamin A and 27,700 U S P XI units of vitamin D per period

the serum was on the border line between a high normal value and a figure indicating slight hypercalcemia, and the phosphorus content was constantly below normal. The phosphatase content on one determination was found to be 51 Bodansky units<sup>10</sup>

When the intake of calcium was low (periods 1 through 7), the amount of calcium in the urine was above the average excretion (0.19 Gm) of normal persons on a similarly low calcium intake found by Bauer, Albright and Aub,<sup>11</sup> although the value is within the range of their normal values (0.03 to 0.47 Gm). The total excretion of calcium per kilogram of body weight per period by our patient during the period of low calcium intake was 0.013 Gm, which is very

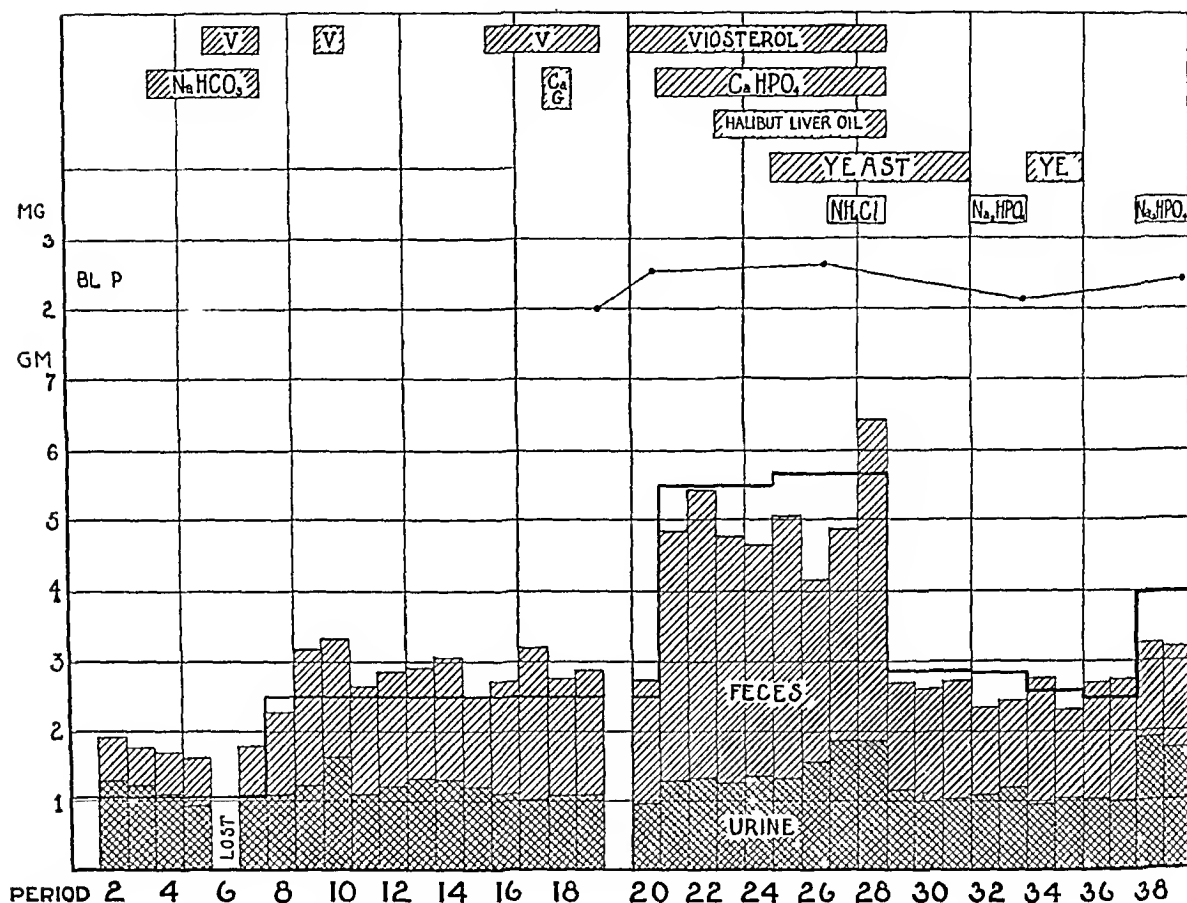


Fig 2—Phosphorus exchange and concentration of phosphorus in the serum during the first metabolism study of Z. K. The heavy line represents the total intake, and each column represents the excretion of phosphorus during one period (three days)

close to the average of 0.012 Gm for the normal subjects studied by the aforementioned investigators. The urinary calcium did not decrease during periods 4, 5, 6 and 7, when large amounts of sodium bicarbonate were administered in order to make conditions optimal for minimal urinary excretion.

<sup>10</sup> Dr. I. G. Macy made this analysis.

<sup>11</sup> Bauer, W., Albright, F., and Aub, J. C. Studies of Calcium and Phosphorus Metabolism. II. The Calcium Excretion of Normal Individuals on a Low Calcium Diet, Also Data on a Case of Pregnancy, *J. Clin. Investigation* 7:75 (April) 1929.

Beginning with period 8 and continuing throughout the remainder of the first study, a diet rich in calcium (800 Gm of whole milk daily) was given. During periods 8 through 17 the urinary excretion of calcium actually decreased slightly, and the fecal excretion was high, averaging 2.97 Gm per period, or 90 per cent of the intake. This high fecal excretion of calcium could have resulted from failure of absorption or from reexcretion of calcium into the intestine. In order to study this question, calcium gluconate was injected intravenously during period 18. In all, 0.54 Gm of calcium equally divided in 12 injections was injected during the three day period. The amount of calcium excreted in the feces during this period did not increase. For this reason it is felt that the high amount of fecal calcium represents unabsorbed calcium. The urine for that period contained 0.67 Gm of calcium, or 0.29 Gm more than the average during the nine previous periods. The remainder of the injected calcium (0.25 Gm) was retained. The phosphorus excreted during this period decreased by an amount almost exactly that needed to form tribasic calcium phosphate with the retained calcium.

It was evident from the study thus far that although the patient was in great need of calcium because of marked skeletal demineralization, when calcium was abundantly supplied in foods (especially milk), he absorbed only a small amount of this element. It was thought that a calcium salt, given as such, might be more readily absorbed. Accordingly, from periods 21 through 28, 14.3 Gm of commercial di-calcium phosphate was ingested in each period, thus increasing the intake of calcium by 3.96 Gm per period. Still only a small amount of calcium was absorbed, and the fecal excretion remained 90 per cent of the intake. The urinary excretion remained essentially unchanged.

Throughout the study large doses of irradiated ergosterol (proved to be potent by studies on rachitic rats) were of no value. Because of the reports of Macy and her associates<sup>12</sup> that positive calcium balance was effected in lactating women by the addition of cod liver oil and yeast to the diet, these supplements were fed. During the periods when yeast was first added, there was greater retention of calcium than at any other time. It was desired to determine whether this improvement resulted from the phosphorus or from the vitamin B that was contained in the yeast. Accordingly, these factors were studied separately while the patient received no calcium except that contained in the diet. During periods 32 and 33 di-sodium hydrogen phosphate was given in an amount sufficient to supply phosphorus equivalent to that in the yeast, and in periods 34 and 35 yeast extract supplying vitamin B equivalent to that in the yeast was administered. No definite benefit resulted from either supplement. Ammonium chloride administered during periods 37 and 38 produced an increase in excretion of calcium both in the urine and in the feces.

Several interesting features of the phosphorus exchange should be pointed out. When the phosphorus intake was low (periods 1 through 7) the excretion was not unusual, but when the dietary phosphorus was raised to 2.49 Gm per period (beginning with period 8), the excretion of phosphorus in the urine remained unchanged, and the fecal excretion of this element was almost twice the urinary excretion. In general, the changes in the phosphorus exchange were similar to those observed in the exchange of calcium, except that when di-sodium hydrogen phosphate was given in abundance during periods 38 and 39, phosphorus was generously absorbed and retained.

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12 Macy, I. G., Hunscher, H. A., McGosh, S. S., and Nims, B. Metabolism of Women During the Reproductive Cycle. III. Calcium, Phosphorus, and Nitrogen Utilization in Lactation Before and After Supplementing the Usual Home Diets with Cod Liver Oil and Yeast, *J. Biol. Chem.* **86**: 59 (March) 1930.



TABLE 3—Second Study of Calcium and Phosphorus Exchange of Z K

Diet	Period	Medication	Nitrogen				Total Urinary				Calcium				Phosphorus			
			Intake, Gm	Out put, Gm	Bal ance, Gm	Ce	Acid, Gm	N/10	Intake, Gm	Urine, Gm	Feces, Gm	Excre tion, Gm	Bal ance, Gm	Intake, Gm	Urine, Gm	Feces, Gm	Excre tion, Gm	Total
Low calcium, 800 calories, calcium phosphorus ratio 0.46	41		15.1	21.52	-6.42	1,572	0.51	0.32	0.60	0.92	0.60	0.92	-0.41	1.42	1.49	0.76	2.25	-0.82
	42		15.1	21.33	-6.23	1,475	0.51	0.42	0.43	0.85	0.43	0.85	-0.34	1.41	1.66	0.53	2.19	-0.78
	43		15.1	21.76	-6.66	1,894	0.51	0.30	0.59	0.89	0.59	0.89	-0.38	1.44	1.57	0.65	2.22	-0.78
	44	Intravenous injection of calcium gluconate (0.54 Gm calcium)	15.1	20.31	-5.21	1,534	1.04	0.57	0.55	1.12	0.55	1.12	-0.08	1.36	1.15	0.65	1.80	-0.41
	45		15.1	19.80	-4.70	1,496	0.50	0.32	0.44	0.76	0.44	0.76	-0.25	1.33	1.48	0.61	2.09	-0.76
High calcium, 800 calories, calcium phosphorus ratio 1.31	46*		15.1	18.69	-3.59	1,503	0.50	0.29	0.66	0.95	0.66	0.95	-0.44	1.26	1.23	0.68	1.96	-0.70
	47		16.98	19.19	-2.21	1,079	3.28	0.31	2.90	3.21	2.90	3.21	0.07	2.62	1.18	1.52	2.70	-0.08
	48		16.98	19.19	-2.21	1,125	3.28	0.51	2.33	2.84	2.33	2.84	0.44	2.62	1.32	1.51	2.83	-0.21
	49		16.98	19.89	-2.91	1,034	3.28	0.36	3.29	3.65	3.29	3.65	-0.37	2.66	1.10	2.37	3.47	-0.81
High calcium, 2,000 calories, calcium phosphorus ratio 1.23	50		25.63	19.88	5.75	1,231	3.43	0.52	2.64	3.16	2.64	3.16	0.27	2.78	1.21	1.45	2.66	0.12
	51		25.63	19.52	6.11	1,010	3.43	0.63	2.91	3.59	2.91	3.59	-0.15	2.78	1.18	1.70	2.83	-0.10
	52		25.63	19.61	6.02	1,061	3.43	0.50	2.91	3.41	2.91	3.41	0.02	2.78	1.25	1.72	2.97	-0.19
	53		25.63	20.10	5.53	1,215	3.43	0.55	2.39	2.94	2.39	2.94	0.53	2.78	1.35	1.52	2.87	-0.09
	54	6 Gm special viosterol†	25.63	19.67	5.96	1,191	3.43	0.60	2.63	3.13	2.63	3.13	0.30	2.78	1.37	1.24	2.61	0.17
	55	6 Gm special viosterol†	35.63	20.57	5.06	1,193	3.43	0.57	2.95	3.52	2.95	3.52	-0.08	2.78	1.45	1.62	3.07	-0.29
	56	6 Gm special viosterol†	25.63	21.24	4.39	1,137	3.43	0.70	2.29	2.99	2.29	2.99	0.44	2.78	1.65	1.07	2.72	0.06
	57	6 Gm special viosterol†	25.63	20.19	5.44	1,317	3.43	0.76	2.41	3.17	2.41	3.17	0.26	2.78	1.52	1.23	2.75	0.03
	58	Same dose of viosterol plus 36 cc 10 per cent hydrochloric acid	25.63	21.81	3.82	1,991	3.43	0.85	2.17	3.02	2.17	3.02	0.41	2.78	1.75	1.20	2.95	-0.17
	59		25.63	22.41	3.22	1,789	3.43	0.98	2.32	3.30	2.32	3.30	0.13	2.78	1.86	1.31	3.16	-0.38
Same dose of viosterol only	60		25.63	23.86	1.77	1,745	3.43	0.99	1.91	2.90	1.91	2.90	0.53	2.78	1.86	0.95	2.81	-0.03
	61	Same dose of viosterol only	25.63	23.75	1.88	1,459	3.43	0.71	2.19	2.90	2.19	2.90	0.53	2.78	2.04	1.27	3.31	-0.53
	62	Same dose of viosterol plus 90 cc 10 per cent calcium chloride	25.63	25.13	0.70	1,735	6.59	1.50	3.78	5.28	3.78	5.28	1.31	2.78	1.76	1.27	3.03	-0.25
	63		25.63	24.88	0.75	2,034	6.59	1.63	4.25	5.88	4.25	5.88	0.71	2.78	1.73	1.55	3.28	-0.50
	64	Same dose of viosterol plus 90 cc 10 per cent calcium chloride	25.63	26.50	-0.87	2,221	6.64	1.86	3.97	5.83	3.97	5.83	0.81	2.84	1.94	0.89	2.83	0.01

\* Two day period Observed results multiplied by 3/2

† Ten times usual strength (2,500 D) Six grams represents 15 mg of pure crystalline vitamin D, or 600,000 U S P XI units of vitamin D

The significant findings in regard to the calcium and phosphorus exchange during this first metabolism study may be summarized as follows (1) high normal concentration of serum calcium, or slight hypercalcemia, (2) high fecal excretion of calcium, not significantly improved by the supplements used, (3) good retention of injected calcium, indicating no difficulty in utilizing calcium once it arrived in the blood stream, (4) constantly low concentration of serum phosphorus, (5) relatively low urinary and high fecal excretion of phosphorus, and (6) ability to absorb and retain satisfactorily phosphorus fed as di-sodium hydrogen phosphate

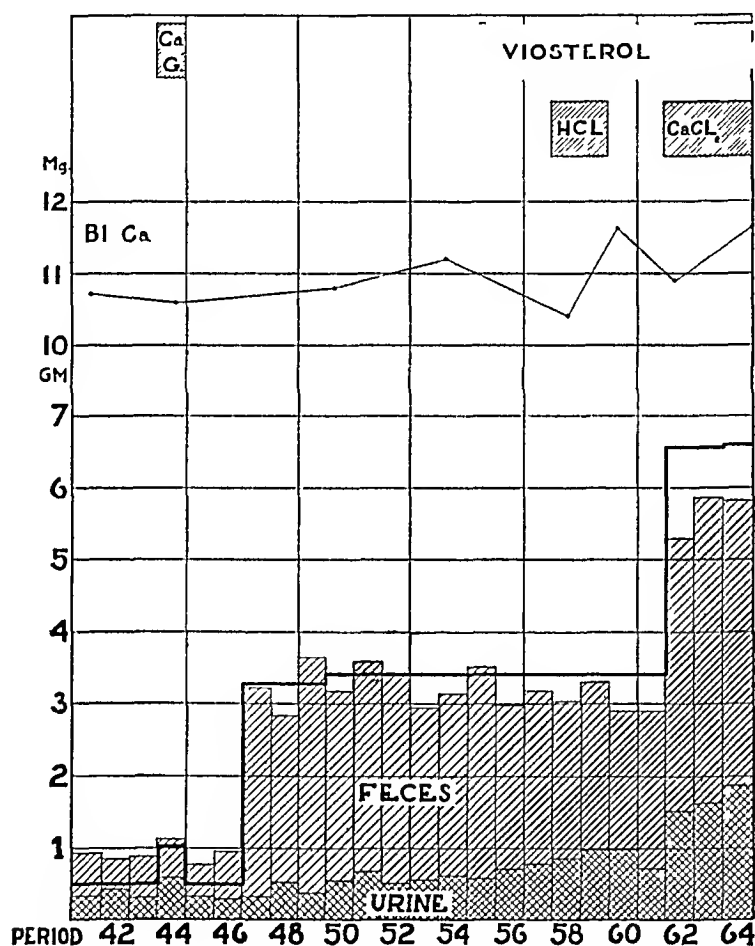


Fig 3—Calcium exchange and concentration of calcium in the serum during the second metabolism study of Z K after roentgen therapy was administered to the hypophysis. The heavy line represents the total intake, and each column represents the excretion of calcium during one period (three days)

*Second Study*—After this first study was completed, the patient was given roentgen therapy to the pituitary gland and discharged. When he returned, two months later, further study of the calcium and phosphorus exchange was made in order to determine whether the roentgen therapy had caused any change in the metabolism of these elements and to test further the effects of certain supplements. The results of this second study appear in table 3 and in charts 3 and 4.

For six periods the patient was fed the same low calcium diet that was used during the first seven periods of the first study. The calcium and phosphorus exchange was essentially the same except for somewhat lower urinary excretion of calcium (the patient's weight was 20 Kg less than at the beginning of the first study). During period 44 the same amount of calcium gluconate was injected as that given in period 18, in exactly the same manner. Owing to the low level of ingestion and excretion of calcium, the disposition of the injected calcium could be more accurately determined. On this occasion the results were exactly the same as those previously noted, the fecal excretion of calcium remained unchanged,

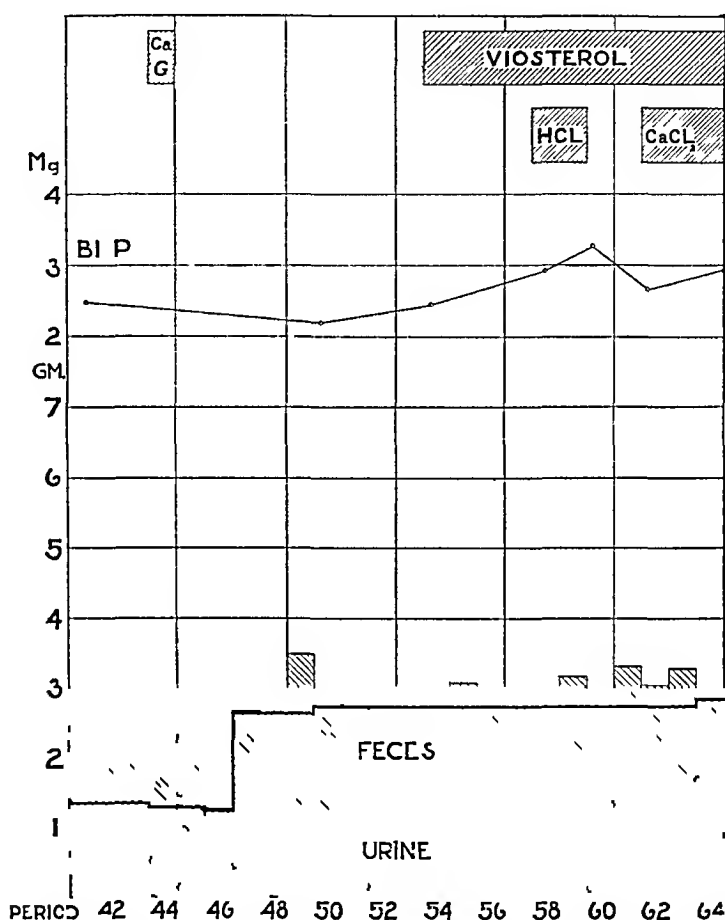


Fig 4—Phosphorus exchange and concentration of phosphorus in the serum during the second metabolism study of Z K after roentgen therapy was administered to the hypophysis. The heavy line represents the total intake, and each column represents the excretion of phosphorus during one period (three days).

the urinary excretion increased, and much of the injected calcium was retained, together with sufficient phosphorus for the formation of tribasic calcium phosphate. This is clearly shown in charts 3 and 4.

During periods 47, 48 and 49 the same high calcium, low calory diet that was used in the latter part of the first study was fed. The exchange of calcium and phosphorus during these periods was essentially the same as that found previously under these conditions. The concentration of calcium in the serum was slightly lower than that during the first study, the concentration of phosphorus was essentially the same. It is obvious, then, that the roentgen therapy had not altered the calcium and phosphorus metabolism in a recognizable way.

Further studies were then carried out. Up to that time the diet had always been undernourishing. In order to learn whether this low calory diet might affect the mineral metabolism, a diet with essentially the same calcium value but supplying the number of calories required for maintenance was fed throughout the remainder of the study. The concentration of calcium and phosphorus in the serum and the urinary excretion of these elements rose slightly. The balance remained essentially the same as when the low calory diet was fed. Beginning with period 54, the patient was fed 6 Gm. of a concentrated solution of viosterol,<sup>13</sup> supplying 600,000 U. S. P. XI units of vitamin D per period. After an initial slight increase, the fecal excretion of calcium decreased slightly, the urinary excretion increased, and the calcium balance was only slightly improved. This effect is essentially the same as that found by Bauer, Marble and Claflin<sup>14</sup> in normal persons. It is interesting to note that the concentration of calcium in the serum decreased and the concentration of phosphorus increased significantly during the administration of vitamin D in this large dosage.

Because an analysis of the gastric juice showed hypo-acidity, the effect of hydrochloric acid was studied. When hydrochloric acid was administered, the concentration of calcium in the serum rose sharply, the concentration of phosphorus rose less noticeably, the fecal excretion of calcium decreased slightly, the fecal excretion of phosphorus remained essentially unchanged and the urinary excretion of these elements was increased.

When calcium chloride was given, the absorption of calcium was better than at any time previously. The concentration of calcium in the serum was increased. The urinary excretion of calcium was doubled, so that, even though the balance was more positive than at any other time, the retention was not great. There was no appreciable change in the phosphorus metabolism.

It was planned to note the mineral metabolism after the cessation of administration of calcium chloride and later of viosterol, but owing to the necessary discharge of the patient these observations could not be made.

#### OBSERVATIONS ON A CONTROL SUBJECT

The interpretation of these findings presents several problems. Published studies of calcium and phosphorus exchange in normal adults are so few and meager that it was thought advisable to control this study by noting the response of a normal young adult to some of the diets and supplements administered to the patient.

Such a control study was conducted on a graduate student living his usual active life. The subject was 26 years old and weighed 64 Kg., the calcium content of the serum was 11.1 mg. per hundred cubic centimeters and the phosphorus content 4.4 mg. The methods of study and of chemical analysis were exactly as described for the patient. The results are shown in table 4 and in charts 5 and 6.

For the first four periods, the control subject was fed a diet identical to that given the patient during periods 50 through 64 (containing 3.4 Gm. of calcium).

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<sup>13</sup> The viosterol was supplied by the Winthrop Chemical Company, Inc.

<sup>14</sup> Bauer, W., Marble, A., and Claflin, D. Studies on the Mode of Action of Irradiated Ergosterol. I. Its Effect on the Calcium Phosphorus and Nitrogen Metabolism of Normal Individuals, *J. Clin. Investigation* **11**: 1 (Jan.) 1932.

TABLE 4—Calcium and Phosphorus Exchange of Normal Control Subject

Diet	Period	Medication	Nitrogen			Total Urinary Acid			Calcium			Phosphorus				
			Intake, Gm	Out put, Gm	Bal ance, Gm	Oe N/10 Acid	Intake, Gm	Urine, Gm	Feces, Gm	Total Excre tion, Gm	Bal ance, Gm	Intake, Gm	Urine, Gm	Feces, Gm	Total Excre tion, Gm	Bal ance, Gm
High calcium, 2,000 calories, calcium phosphorus ratio 1.23	1		25.63	34.02	-8.39		3.40	0.26	2.77	3.03	0.37	2.91	2.00	1.02	3.62	-0.71
	2		25.63	33.27	-7.64		3.40	0.35	2.83	3.18	0.22	2.87	2.09	1.17	3.86	-0.99
	3		25.63	31.45	-5.82		3.40	0.30	2.03	2.38	1.02	2.76	2.28	0.67	2.95	-0.19
	4		25.63	29.74	-4.11		3.40	0.33	3.65	3.93	-0.33	2.66	2.45	1.32	3.77	-1.11
High calcium, 3,200 calories, calcium phosphorus ratio 0.95	5		34.0	35.73	-1.73		3.55	0.29	2.67	2.96	0.59	3.80	2.47	1.45	3.92	-0.12
	6		34.0	35.34	-1.34		3.55	0.36	2.66	3.02	0.53	3.78	2.39	1.43	3.82	-0.04
	7		34.0	36.89	-2.89		3.55	0.41	2.86	3.27	0.28	3.87	2.47	1.46	3.93	-0.06
	8	Calcium hydrogen phosphate 14.3 Gm	34.5	34.43	0.07		7.51	0.54	6.82	7.36	0.15	6.50	3.54	3.32	6.86	-0.36
	9	Calcium hydrogen phosphate 14.3 Gm	34.5	*	*		7.51	*	7.13	*	*	6.50	*	3.31	*	*
	10	Calcium hydrogen phosphate 14.3 Gm	34.5	34.00	0.50		7.51	0.43	6.54	6.97	0.54	6.50	3.26	2.43	5.69	0.81
	11	Calcium hydrogen phosphate 14.3 Gm	34.5	33.00	-3.50		7.51	0.50	6.46	6.96	0.55	6.70	3.66	2.04	5.70	1.00
	12	Calcium hydrogen phosphate 14.3 Gm	34.0	33.04	0.96	1,973	3.55	0.33	4.42	4.75	-1.20	3.71	2.35	2.33	4.63	-0.97
	13	36 cc 10 per cent hydrochloric acid	34.0	35.00	-1.00	2,285	3.55	0.37	3.00	3.37	0.18	3.77	2.52	1.70	4.22	-0.45
	14	36 cc 10 per cent hydrochloric acid	34.0	33.40	0.60	2,410	3.55	0.41	2.47	2.88	0.67	3.71	2.51	1.13	3.64	0.07
	15		34.0	34.66	-0.66	1,894	3.55	0.40	3.19	3.59	-0.04	3.75	2.64	1.53	4.18	-0.43
	16	90 cc 10 per cent calcium chloride	34.0	35.31	-1.31	2,122	6.71	0.81	5.70	6.51	0.20	3.78	2.19	1.54	3.73	0.05
	17	90 cc 10 per cent calcium chloride	34.0	35.36	-1.36	2,615	6.71	0.71	4.85	5.56	1.15	3.78	2.15	1.33	3.48	0.30
	18		34.0	35.85	-1.85	2,433	3.55	0.44	4.18	4.62	-1.07	3.82	2.69	1.71	4.40	-0.58
	19		34.0	31.20	2.80	1,897	3.55	0.46	3.26	3.72	-0.17	3.71	2.29	1.63	3.92	-0.21

\* Part of the urine was lost

The caloric value of the diet was considerably below that required to keep him in energy balance. During that time the urinary excretion of calcium was slightly less than that of Z K while he was on this diet but was equal to the urinary excretion of Z K when he was fed an undernourishing diet with a similar calcium content. The fecal excretion of calcium was essentially the same as that of the patient when fed this diet. The calcium balance was slightly positive.

The phosphorus exchange was decidedly different from that observed in Z K. The urinary excretion of phosphorus was more than twice as great as the fecal secretion, which is the usual partition of this element in the excreta of normal persons. This is in contrast to the patient's excretion of phosphorus, most

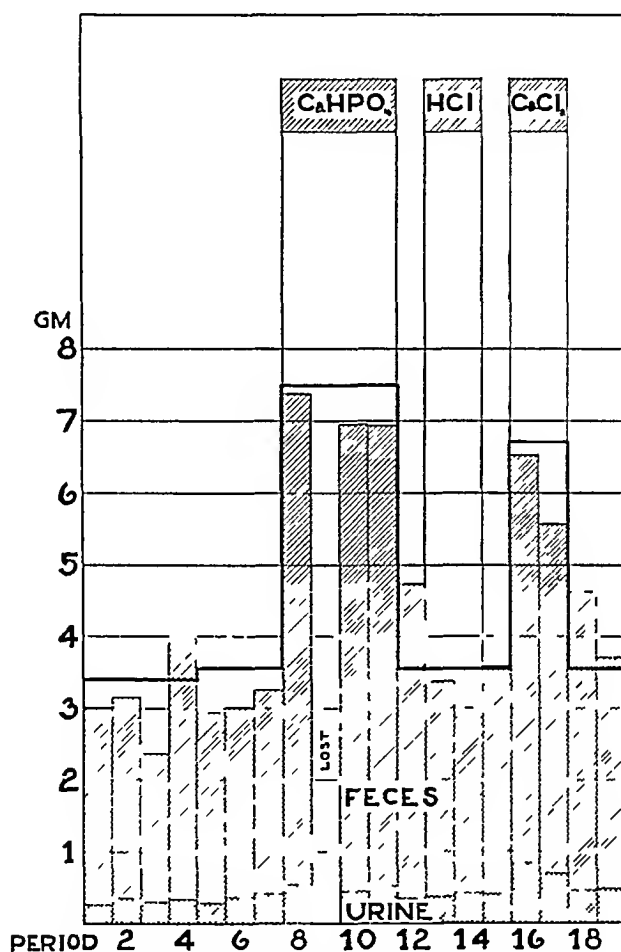


Fig 5—Calcium exchange of the normal control subject. The heavy line represents the intake, and each column represents the excretion of calcium during one period (three days).

of which was in the feces. Moreover, the excretion of phosphorus in the urine of the control subject was twice as great as that of the patient when he was fed the same diet.

Because this diet was undernourishing for the control subject, beginning with period 5 and continuing throughout the remainder of the study, a diet was fed which supplied essentially the same amount of calcium with the number of calories required for maintenance. The calcium and phosphorus exchange was essentially unchanged.

When calcium hydrogen phosphate was fed in amounts equivalent to those fed the patient, the urinary excretion of calcium rose significantly (distinctly different

from the patient's response), the fecal excretion and the calcium balance, however, were similar to those of the patient. Likewise, the urinary excretion of phosphorus increased decidedly, the fecal excretion was less than that of the patient, and the phosphorus balance was positive. These observations indicate that the control subject absorbed more of the calcium hydrogen phosphate than did the patient.

When hydrochloric acid was fed to the control subject in an amount equal to that fed to Z K, the acidity of the urine and the urinary excretion of calcium were increased by much smaller amounts than in the patient. The phosphorus exchange was not affected.

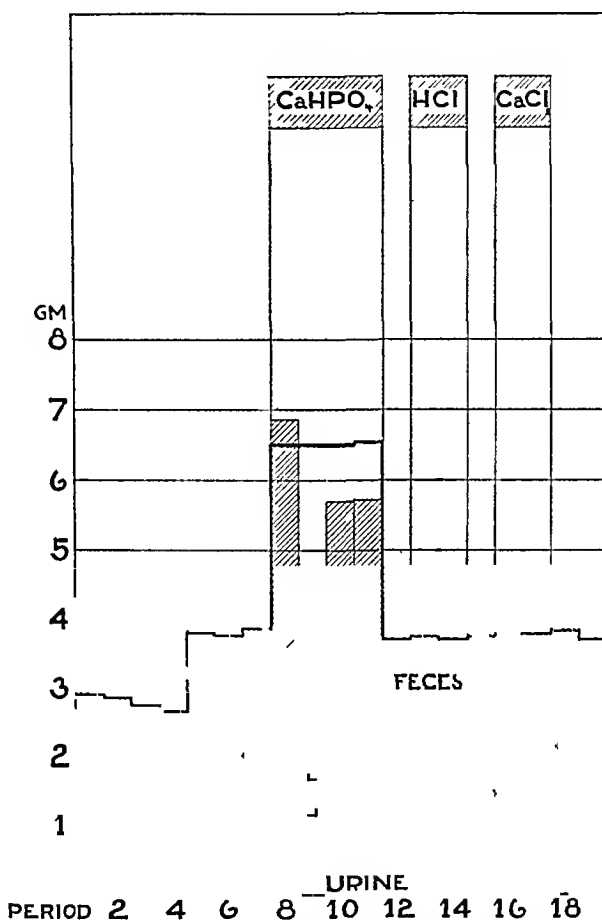


Fig 6—Phosphorus exchange of the normal control subject. The heavy line represents the intake, and each column represents the excretion of phosphorus during one period (three days).

Calcium chloride fed to the control subject in exactly the same way as it was given to the patient caused only a slight rise in the acidity of the urine and a smaller increase in urinary excretion of calcium than was found for the patient. The urinary excretion of phosphorus decreased slightly, and the phosphorus balance became slightly positive.

#### COMMENT

When the mineral exchange of the patient is compared with that of the control subject, it is noted that the calcium metabolism of the patient differed in the following ways. The urinary excretion of calcium

at times was slightly greater, it did not increase when calcium hydrogen phosphate was administered, but there was a greater increase when hydrochloric acid and calcium chloride were taken. Even more striking differences are noted in the phosphorus metabolism. The concentration of phosphorus in the patient's serum was constantly low, the urinary excretion of phosphorus was small, and there was a reversal of the normal partition of phosphorus in the urine and feces.

When the mineral metabolism of our patient is compared with that existing in a state of hyperparathyroidism, several noteworthy differences are evident. Bauer<sup>15</sup> pointed out that hyperparathyroidism is characterized by (1) an elevated concentration of serum calcium, (2) a decreased concentration of serum phosphorus and (3) increased urinary excretion of both calcium and phosphorus. Albright<sup>16</sup> showed that the primary effect of the parathyroid hormone, however, is to increase the urinary excretion of phosphorus by lowering the renal threshold for the excretion of this element. This same investigator<sup>17</sup> also pointed out that patients with hyperparathyroidism have no difficulty in absorbing calcium and that if there is a liberal ingestion of this element enough calcium is absorbed so that the calcium balance becomes positive despite the resultant increase in urinary excretion.

With these facts in mind, it is at once evident that the mineral metabolism in our patient is not characteristic of hyperparathyroidism. In keeping with this, the parathyroid bodies showed nothing histologically to suggest hyperactivity: they were not enlarged, no zones of proliferation or adenomas were present, they were grossly infiltrated with fat.

It is noteworthy that in the reports of verified cases of pituitary basophilism (table 1) there is no instance of hypercalcemia. In all cases in which skeletal decalcification was present concentration of serum phosphorus was low.

One of the most interesting features of the mineral metabolism in our patient was the failure to absorb more than small amounts of calcium even though there was great need for it. Bauer<sup>18</sup> has shown that

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15 Bauer, W. Hyperparathyroidism—A Distinct Disease Entity, *J Bone & Joint Surg* **15** 135 (Jan) 1933.

16 Albright, F., Bauer, W., Ropes, M., and Aub, J. C. Studies of Calcium and Phosphorus Metabolism. IV. The Effect of the Parathyroid Hormone, *J Clin Investigation* **7** 139 (April) 1929.

17 Albright, F., Bauer, W., Clafin, D., and Cockrill, J. R. Studies in Parathyroid Physiology. III. The Effect of Phosphate Ingestion in Clinical Hyperparathyroidism, *J Clin Investigation* **11** 411 (March) 1932.

18 Bauer, W., and Marble, A. Studies on the Mode of Action of Irradiated Ergosterol. II. Its Effect on the Calcium and Phosphorus Metabolism of Individuals with Calcium Deficiency Diseases, *J Clin Investigation* **11** 21 (Jan) 1932.



certain patients with calcium deficiency diseases can be caused to absorb and retain large amounts of calcium when a potent preparation of vitamin D is administered. This supplement, even when fed in huge doses to our patient, caused little, if any, benefit. The unusual mineral metabolism and skeletal decalcification cannot be due, therefore, to vitamin D deficiency.

The persistence in our patient of epiphyses which normally should have disappeared certainly indicates that some abnormality of the calcium and phosphorus metabolism other than simple osteoporosis exists.

#### CONCLUSIONS

The calcium and phosphorus exchange in a case of verified pituitary basophilism is reported. The findings considered most noteworthy are (1) a low concentration of serum phosphorus, (2) a low urinary and a high fecal excretion of phosphorus, (3) failure to absorb sufficient calcium and phosphorus to allow retention of appreciable amounts of these elements, even though there was great need for calcium phosphate in the skeleton, (4) failure of vitamin D and other supplements to increase appreciably the absorption and retention of calcium and (5) good utilization of calcium injected intravenously.

This patient's metabolism of calcium and of phosphorus is not characteristic of hyperparathyroidism.

A complete understanding of the abnormalities of the mineral metabolism in cases of pituitary basophilism must await further studies.

# THE OBESITY AND ENERGY EXCHANGE IN A VERIFIED CASE OF PITUITARY BASOPHILISM

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AND

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Obesity is frequently observed in patients who have lesions of the hypophysis. The adiposity associated with Frohlich's syndrome is well known. Cushing<sup>1</sup> recently described a clinical syndrome resulting from basophil adenoma of the pituitary gland. One of the features of this syndrome is adiposity, which is said to be confined characteristically to the face, neck, thorax and abdomen, sparing the extremities. The abdomen is usually protuberant and often pendulous.

The feeling is prevalent that the obesity associated with dyspituitarism results from some unusual metabolic disturbance, which in a mysterious way causes an increased synthesis and deposition of body fat. The significance of hypercholesteremia, commonly present in cases of pituitary basophilism, has been variously interpreted. Kraus<sup>2</sup> suggested that a disturbance of fat metabolism with an associated hypercholesteremia may be the fundamental abnormality in Cushing's disease and that as a result of this metabolic disturbance lesions develop in the adenohypophysis (excess basophilia or basophil adenoma) and in the adrenal bodies (cortical hyperplasia or adenoma) which in turn produce the striking clinical manifestations of this syndrome.

In a previous paper<sup>3</sup> we reported a case of Cushing's disease showing the classic clinical syndrome, in which the diagnosis was verified by the finding of a basophil adenoma of the adenohypophysis at post-

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From the Department of Internal Medicine, Medical School, University of Michigan

1 Cushing, H. The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism), *Bull Johns Hopkins Hosp* **50** 137 (March) 1932

2 Kraus, E. J. Relation of Chromophil Cells of the Hypophysis to Carbohydrate, Fat and Cholesterol Metabolism, Study of Cushing's Pituitary Basophilism, *Med Klin* **29** 449 (March) 1933

3 Freyberg, R. H., Barker, P. S., Newburgh, L. H., and Collier, F. A. Pituitary Basophilism (Cushing's Syndrome). Report of a Verified Case, with a Discussion of the Differential Diagnosis and Treatment, *Arch Int Med*, this issue, p 187

mortem examination The patient was under observation for the greater part of a year, during which time various metabolic studies were made The calcium and phosphorus exchange in this patient is described in a separate paper<sup>4</sup> The purpose of this communication is to report the results of a study of the energy exchange in this patient

In normal persons, when the outflow of energy exceeds the inflow, the difference is furnished by the oxidation of body tissues according to well established principles After the first few days on a reduction diet, the caloric deficit is met by the combustion of body fat and by a small amount of body protein if the diet is low in protein The amount of body protein burned can be readily determined if the amount of dietary and excretory nitrogen is known The total caloric deficit minus that portion furnished by the combustion of body protein is met by the combustion of body fat Knowing the calorific value of the body protein and fat burned, one can determine the weight of each of these materials destroyed This weight, together with the weight of the water physiologically attached to the tissues, which is liberated when the tissues are burned, represents the total loss of weight of the subject

#### OBSERVATIONS ON THE PATIENT

The inflow of energy was kept constant and small in our patient by a diet supplying only 890 calories daily The composition of the diet was exactly the same day after day The outflow of energy was determined for nine successive twenty-four hour periods by the method described by Newburgh and his associates<sup>5</sup> Assuming that the energy expenditure continued at a rate equal to the average for the nine days during which it was measured, it was predicted that at the end of fifty-four days (the length of time the patient was fed this same diet without interruption) the weight should be reduced by 8,376 Gm The actual record of the weight showed the loss to be 8,398 Gm, or 22 Gm more than the predicted loss based on normal energy exchange

Figure 1 shows graphically the actual and predicted weights during this period of study It is seen that the actual loss of weight varies only slightly from the straight line of predicted loss of weight This exceptionally good agreement exists because not only was the caloric intake constant but the mineral and fluid intake was identical day after day, and the activity of the patient was essentially the same each day Consequently, the error experienced was less than 0.3 per cent

This excellent agreement between the actual weight and the weight predicted on the basis of normal disposition of energy-supplying materials indicates certainly that the energy exchange in this patient during the period of weight reduction was entirely normal There was, therefore, no unusual metabolic feature acting

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4 Freyberg, R. H., and Grant, R. L. Calcium and Phosphorus Metabolism in a Verified Case of Pituitary Basophilism, *Arch Int Med*, this issue, p. 213

5 Newburgh, L. H., Wiley, F. H., and Lashmet, F. H. A Method for the Determination of Heat Production over Long Periods of Time, *J Clin Investigation* **10** 703 (Oct.) 1931

as the cause of obesity. He became obese because the inflow of energy exceeded the expenditure of energy, the excess energy being stored in the body in the form of fat.

The appearance of this patient at the time of admission gave the impression that the adiposity was largely confined to the head, neck and trunk. After the patient had lost 22.5 Kg of adipose tissue, the unusually prominent chest and abdomen had been little altered and had not diminished in size any more than had the extremities (figs 2 and 3). Hence the disproportionate enlargement of the trunk could not have been due simply to adiposity. A lateral roentgenogram of the chest shows the actual reason for the abnormal configuration (fig 4). The thinness of the vertebral bodies allowed a shortening of the spine and kyphosis. As a result, the thorax had a greatly increased anteroposterior diameter.

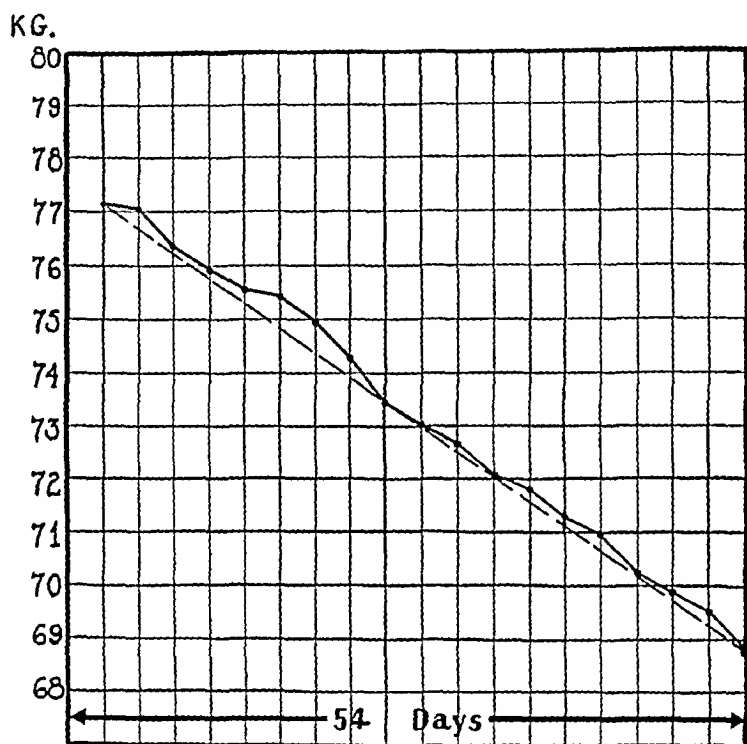


Fig 1—The predicted and actual weight curves over a fifty-four day period of undernutrition. The broken line represents the predicted weight, and the solid line indicates the actual weight. The predicted total loss was 8,376 Gm, and the actual loss was 8,398 Gm.

Another interesting physical finding in this patient was the apparent absence of scrotum and penis noted on admission. In this respect, the appearance of the patient closely resembled that characteristic of Frohlich's syndrome. When the patient's weight was reduced, there was seen to be a definite but small penis and small gonads contained in a normal-appearing scrotum (fig 5). The apparent absence of external genitalia in this case is seen to be due chiefly to the fact that they were hidden in the abundant pubic fat.

The basal metabolic rate was  $-2$  per cent (a normal value) at the beginning of the study. After three months on the reduction diet, the rate of basal metabolism decreased to  $-24$  per cent, the usual response to undernutrition.

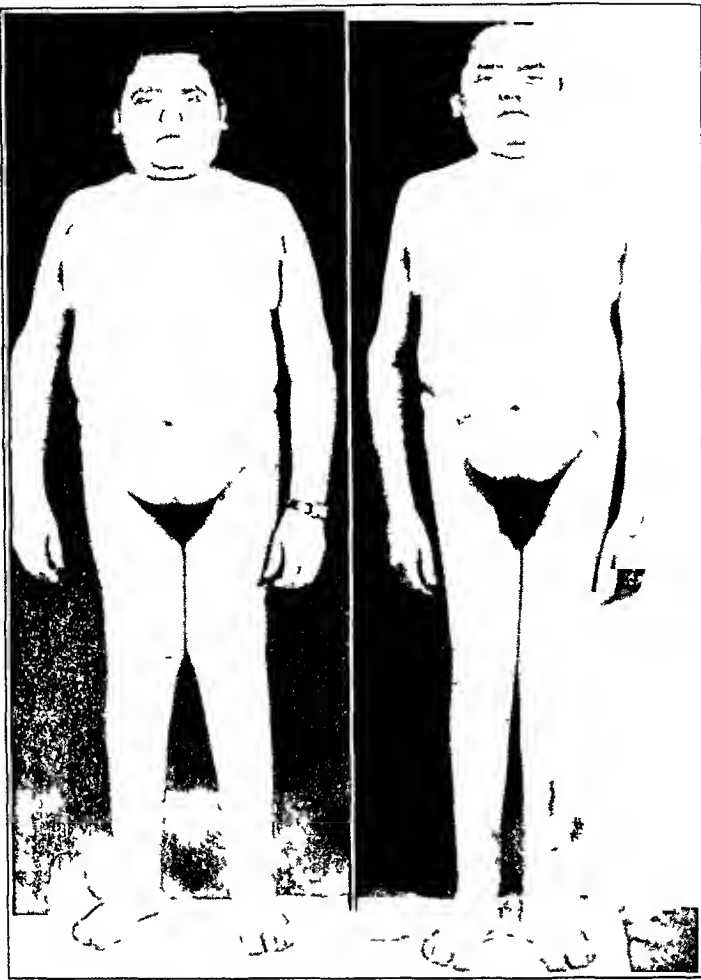


Fig 2—Front view of the patient before and after he lost 225 Kg in response to undernutrition



Fig 3—Lateral view of the patient before and after he lost 225 Kg in response to undernutrition

Hypercholesteremia did not exist in our patient. The concentration of cholesterol in whole blood was 165 mg per hundred cubic centimeters.<sup>6</sup> Duplicate analyses of a mixture of equal portions of cerebrum and cerebellum removed at autopsy



Fig 4—A lateral roentgenogram of the chest, showing the increased antero-posterior diameter, the horizontal course of the ribs, the high diaphragm and the transverse position of the heart

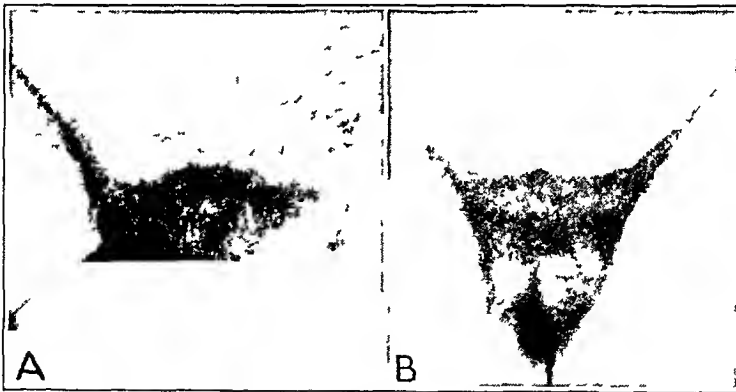


Fig 5—The genitalia, *A*, hidden in pubic fat at the time of admission and, *B*, plainly visible after reduction of weight

showed 234 gm of cholesterol per hundred grams of tissue. This is a normal value.

<sup>6</sup> All determinations of cholesterol were made by a modification of the digitonin precipitation method of Windaus.

## CONCLUSIONS

In a patient with verified pituitary basophilism undernutrition caused loss of weight exactly as predicted for a normal person, thus demonstrating a normal energy exchange and the absence of any unusual metabolic feature as the cause of the obesity

The unusual configuration in this patient was chiefly the result of an underlying skeletal deformity and was not primarily due to adiposity

# CHRONIC PULMONARY INFECTION DUE TO THE FRIEDLANDER BACILLUS

## FURTHER OBSERVATIONS

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In previous publications<sup>1</sup> from this hospital, my associates and I described the clinical and roentgenologic features of three cases of pneumonia with recovery and expressed the belief that the organism responsible for the production of the pulmonary lesion was the Friedlander bacillus (*Bacillus mucosus-capsulatus*). In two of these cases the onset suggested bronchopneumonia, in one, lobar pneumonia. The temperature fell by lysis in all cases, and in all the total leukocyte count tended to be lower than that seen in the usual case of pneumococcal lobar pneumonia. The outstanding finding on physical examination was the extreme indolence of the lesion in the lung. We expressed the belief that there are characteristic roentgen signs which serve to differentiate this condition from other pulmonary infections. Several months after the acute infection had subsided, evidence of pathologic change in the lung could still be demonstrated both by physical and by roentgen examination. On the basis of the studies reported at that time, we expressed the belief that there is a chronic form of pulmonary disease caused by *B. mucosus-capsulatus*. We further expressed the belief that in many respects the chronic form of this disease simulated chronic pulmonary tuberculosis and therefore that in cases of suspected tuberculosis in which the sputum had never shown *Bacillus tuberculosis* it should be examined for *B. mucosus-capsulatus*.

My purpose in the present paper is twofold: first, to present follow-up data on these three original cases, and, second, to record observations made by my associates and me on a fourth nonfatal case in which we succeeded in isolating the Friedlander bacillus in a culture of the blood during the height of the pneumonia.

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From the medical clinic, Hospital of the University of Pennsylvania.

1 (a) Stengel, A., Kornblum, K., and Collins, L. H., Jr. Friedlander's Pneumonia, Clinical and Roentgenological Study of Cases with Special Reference to a Chronic Form Simulating Pulmonary Tuberculosis, *Tr. A. Am. Physicians* **43** 326, 1928. (b) Kornblum, K. The Roentgen Ray Diagnosis of Pulmonary Infections with Friedlander's Bacillus, *Am. J. Roentgenol.* **19** 513, 1928. (c) Collins, L. H., Jr., and Kornblum, K. Chronic Pulmonary Infection Due to Friedlander's Bacillus. A Clinical and Roentgenologic Study, *Arch. Int. Med.* **43** 351 (March) 1929.



## OBSERVATIONS ON CASES

Of the original cases, we have the most complete data on case 1

CASE 1—J A is now 58 years of age. He was admitted to the hospital in 1927, in a diabetic coma, with an illness that already has been described<sup>1c</sup>. In the intervening years he has attended the outpatient department of the hospital for the treatment of his diabetes, and both his diabetic and his pulmonary status have been followed. During these years he has suffered neither from frequent colds nor from additional attacks of pneumonia. At the time of writing he has no pulmonary symptoms. Physical examination of the chest reveals moderate impairment in the percussion note over the right side of the chest anteriorly. Over the lower half of the right lung anteriorly and in the right axilla many fine râles are heard. At the base of the right lung, posteriorly the expiratory phase of respiration is prolonged, but no râles are heard.

The roentgen studies of this patient, extending from 1927 to 1934, have been of particular interest. In a previous paper<sup>1c</sup> we included five roentgenograms of this patient's lungs, showing (1) the primary stage of bronchopneumonia, (2) the pseudolobar stage, (3) the stage of multiple abscess and cavity formation, (4) the stage of fibrosis, revealing the appearance of the lungs at the time of the patient's discharge from the hospital and (5) the chronic stage, approximately ten and one-half months after the onset of the acute pneumonia.

Figure 1 A shows the chest on March 10, 1933. There had been marked improvement in the appearance of the chest since the examination in 1927. There still remained however, a definite diffuse fibrosis throughout the right lung. Figure 1 B shows the chest on Sept 20, 1933. At that time the right lung was the seat of fibrous strands, the crossing of which simulated thin-walled cavities. The right dome of the diaphragm was elevated and wavy, largely in the anterior portion of the chest, indicating that the greater part of the pathologic process was in the upper and middle lobes. Figure 1 C, taken on June 19, 1934, showed that the condition of the chest was essentially the same as on Sept 20, 1933. The right lung was the seat of many fibrous strands. There was no evidence of cavitation. There was marked peaking of the dome of the diaphragm on the right side. In summary, the lungs of this patient showed chronic changes by clinical and roentgenologic examination which we believe are attributable to acute pneumonia produced by *B. mucosus-capsulatus* in 1927.

CASE 2—M P, a thin white woman, was admitted to the hospital on Feb 9, 1927, and was discharged on April 6, 1927. At that time she was 50 years of age. The last contact that we had with this patient was six and one-half months after her discharge from the hospital. At that time, however, physical examination still revealed signs at the base of the left lung and roentgen examination<sup>2</sup> showed a cavity remaining in the region of the old abscess with fibrosis in the base of the left lung.

Because of the death of the original referring physician and of the patient's relatives we have been able only recently to secure follow-up information concerning this patient. Through the kindness of the Mount Sinai Hospital of Philadelphia we obtained the following data in a letter of July 10, 1934: "M P, aged 51, was admitted to this hospital on Feb 16, 1929, and died on Feb 17, 1929, with a final diagnosis of thrombosis involving the vessels of the left lower extremity and probably also the left iliac vein following sepsis (confirmed by postmortem examination)."

"The patient was admitted on the evening of Feb 16 1929 Three weeks before admission an acute sore throat developed, which the family said was diagnosed by a physician as diphtheria and for which she received antitoxin Two weeks before admission the patient became irrational, and because she became more toxic and appeared moribund, another physician was called, who sent her to this hospital

"Examination revealed a white woman, extremely toxic, very irrational and markedly cyanotic, the left pupil was smaller than the right and reacted sluggishly to light, the throat was slightly congested, but no membrane was visible,

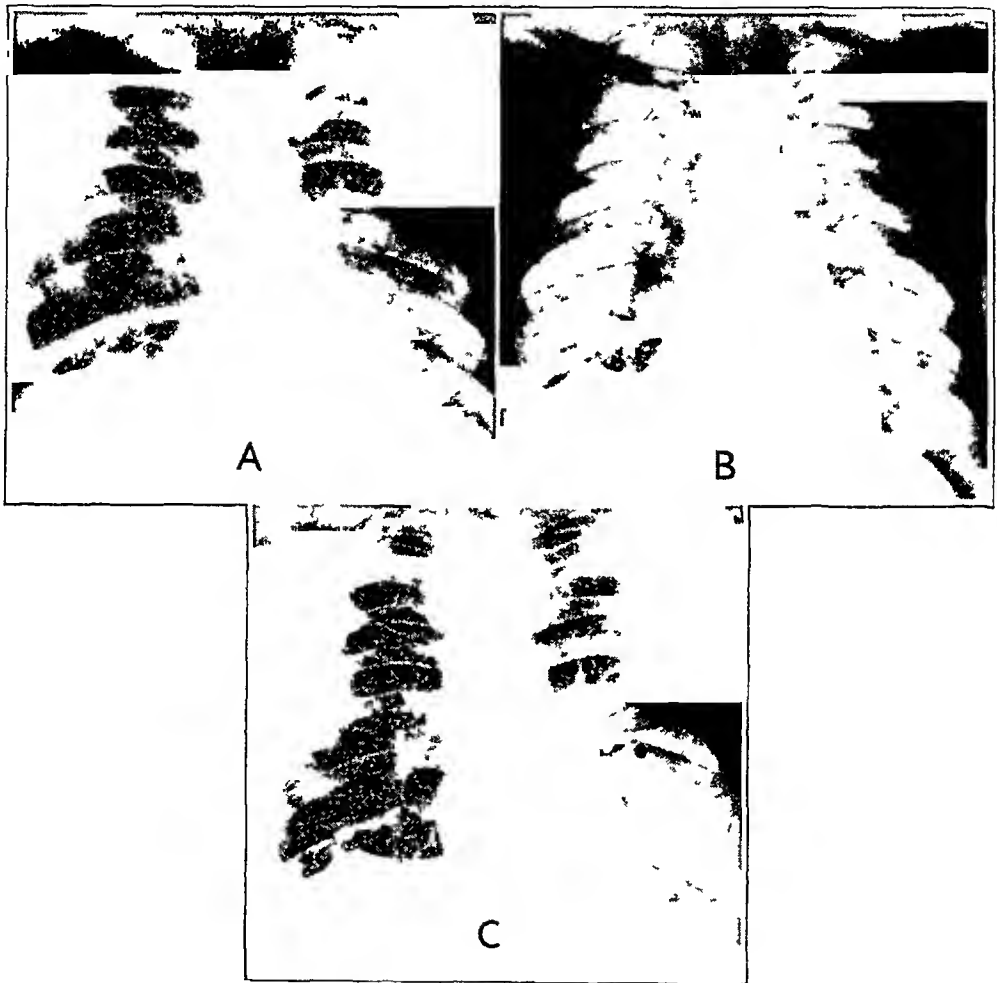


Fig 1 (case 1) —*A*, roentgenogram taken on March 10, 1933, showing a marked improvement in the appearance of the chest since the last examination in 1927 There still remained, however, a definite fibrosis throughout the right lung *B*, roentgenogram taken on Sept 20, 1933 The right lung was the seat of fibrous strands, the crossing of which simulated thin-walled cavities *C*, roentgenogram taken on June 19, 1934 The right lung was the seat of many fibrous strands No evidence of cavitation was present Marked peaking of the dome of the diaphragm was present on the right side

the lungs were clear, the heart was very rapid, the rhythm was irregular and the first and second sounds approximated each other, the blood pressure was 90 systolic and 50 diastolic, the abdomen was normal except for edema and tenderness of the left lower quadrant, the entire left lower extremity was

edematous and was about one and one-half times the diameter of the right, there was a beginning area of gangrene of the left foot, the dorsalis pedis artery of the left foot was not palpable, on the right side the pulse was good. Examination of the pelvis failed to reveal any palpable mass that would produce pressure on the return circulation.

"Laboratory studies on admission revealed a normal hemoglobin content and red cell count, 18,000 leukocytes per cubic millimeter, with 78 per cent polymorphonuclears, a highly concentrated urine, with an occasional white cell and loaded with hyaline and granular casts, 33 mg of urea nitrogen per hundred cubic centimeters, a normal sugar content of the blood, normal serologic reactions, and a spinal fluid cell count of 18 leukocytes per cubic millimeter.

"The temperature on admission was 103 F, the pulse rate was 150 and the respiratory rate was 40. The patient died eighteen hours after admission, with a temperature of 107 F and a pulse too rapid to count."

The following are excerpts from the autopsy notes: "Acute splenitis was present, and there was cloudy swelling of the liver. The vena cava inferior and the right iliac vein were empty. The left iliac vein was filled with thrombus. Histologic examination of other organs revealed evidence of acute passive congestion and cloudy swelling. A culture of blood from the heart showed no growth after forty-eight hours. The left lung contained no adhesions. The pleura presented no abnormalities. No consolidations were felt. The cut surface presented a great deal of chronic passive congestion. The right lung showed the same changes."

From the standpoint of our particular interest in the pathologic changes in this patient, it is unfortunate that neither the paraffin blocks nor the lungs were saved. Also the autopsy notes do not indicate the portion of the lung from which tissue was removed for histologic examination. Consequently, we are left without information concerning the eventual fate of the abscess in the lower lobe of the left lung.

CASE 3—T. M., a well developed Negro aged 43, was admitted to the hospital on March 5, 1927, with the history and symptoms of acute lobar pneumonia. He was discharged on May 5, 1927, to spend a few weeks at a home for convalescents before returning to work as a laborer. This man belonged to the floating Negro population that comprises a portion of the southern section of this city. A painstaking search, both in Philadelphia and in Virginia, whence he originally came, has failed to locate him.

In a former paper,<sup>3</sup> we stated that to the best of our knowledge, in all cases of pneumonia due to Friedlander's bacillus in which the organism has been recovered from the circulating blood the condition has ended fatally. It is true that in our cases reported at that time blood cultures remained sterile, but the repeated recovery of this organism in profuse growth from the sputum together with the clinical and roentgenologic features of these cases, we felt, justified the conclusion that the pulmonary lesions had been produced by the Friedlander bacillus.

With the passage of time we have retained confidence in this conclusion because of data obtained in our fourth case, in which *B. mucosus-capsulatus* was recovered from the blood stream during the acute stage of the pneumonia.

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3 Collins and Kornblum,<sup>1c</sup> p. 360.

CASE 4—J J, a well developed Italian laborer, aged 63, was admitted to the hospital on Dec 18, 1932, and was discharged on Feb 16, 1933. His chief complaint on admission was pain in the right side of the chest. Apparently he had been well until four days before admission, when, without any history of exposure or trauma, he arose in the morning and had a chill which lasted about an hour.

During that time he felt alternately hot and cold. He spent the remainder of that day in bed, and when he awoke on the following day he had severe pain in the entire right side of the chest, anteriorly and posteriorly. Also there was great difficulty in breathing, with much coughing productive of large amounts of bloody sputum. At that time his physician said that his lungs were congested. During the two following days his general condition became steadily worse, and when delirium supervened his physician decided to send him to the hospital at once. We calculated that he was admitted on the fifth day of his illness.

This patient had never had pneumonia previously and apparently was not susceptible to other forms of disease of the respiratory tract. The past medical and the family history were irrelevant. He had always been a heavy drinker of wine.

At the time of his admission to the hospital the temperature was 101.8 F, the pulse rate 120 and the respiratory rate 40. The blood pressure was 110 systolic and 60 diastolic. At that time the patient did not appear particularly dyspneic, though there was distinct cyanosis of the cheeks, ears and lips. He did not appear to have pain in the chest. The chest was emphysematous, with a markedly obtuse subcostal angle. Expansion was fair, being slightly restricted on the right side. There was marked dullness to percussion, both anteriorly and posteriorly. The percussion note over the entire left lung seemed hyperresonant. Over the upper lobe of the right lung the breath sounds were tubular in quality, and over the anterior aspect of this lobe an occasional crackling râle was heard. At the base of the right lung posteriorly there were heard many fine crackling râles. The tentative diagnosis was pneumonia of the upper lobe of the right lung with possible involvement of the lower lobe.

On Dec 19, 1932, the day following admission, the leukocytes numbered 12,800, of which 85 per cent were polymorphonuclears. Abdominal distention was marked. Cyanosis of the lips and nail beds was slight. The patient appeared drowsy at this time and remained so for several days thereafter. The abdominal distention was controlled by enemas and by repeated doses of physostigmine.

On December 2 physical signs of consolidation of the upper lobe of the right lung were still definite. It was concluded after physical examination that the middle and lower lobes were not involved. On December 22 the leukocyte count was 18,700, with 91 per cent polymorphonuclear neutrophils, 10 per cent being filamented forms and 81 per cent nonfilamented forms, 6 per cent lymphocytes and 3 per cent mononuclears. The Wassermann reaction of the blood was negative.

At that time there was only a moderate amount of cough, productive of grossly blood-tinged sputum. Culture of this sputum showed *B. mucosus-capsulatus* (Friedlander) in large numbers as the predominant organism. A blood culture taken on December 19 showed a pure culture of *B. mucosus-capsulatus*. As far as could be determined bacteriologically, the organisms found in the sputum and those isolated from the blood were identical.

Roentgenograms of the chest made by Dr. E. P. Pendergrass on December 23 (fig. 2A) were interpreted as follows: "Lobar pneumonia is present in the

upper lobe of the right lung There is consolidation of this lobe, possibly beginning in the lower lobe, as the dome of the diaphragm is elevated posteriorly, having the appearance of being perfectly flat with a fluid level I think, however, that this is due to a lack of aeration in the lower lobe"

A second blood culture, taken three days after the first one, was sterile The roentgenogram of the chest taken on Dec 27, 1932 (fig 2 *B*), was interpreted by Dr Pendergrass as follows "Friedlander's pneumonia is present There is resolving pneumonia in the upper lobe of the right lung The irregular rarefactions suggest the formation of cavities" During these days the patient remained in

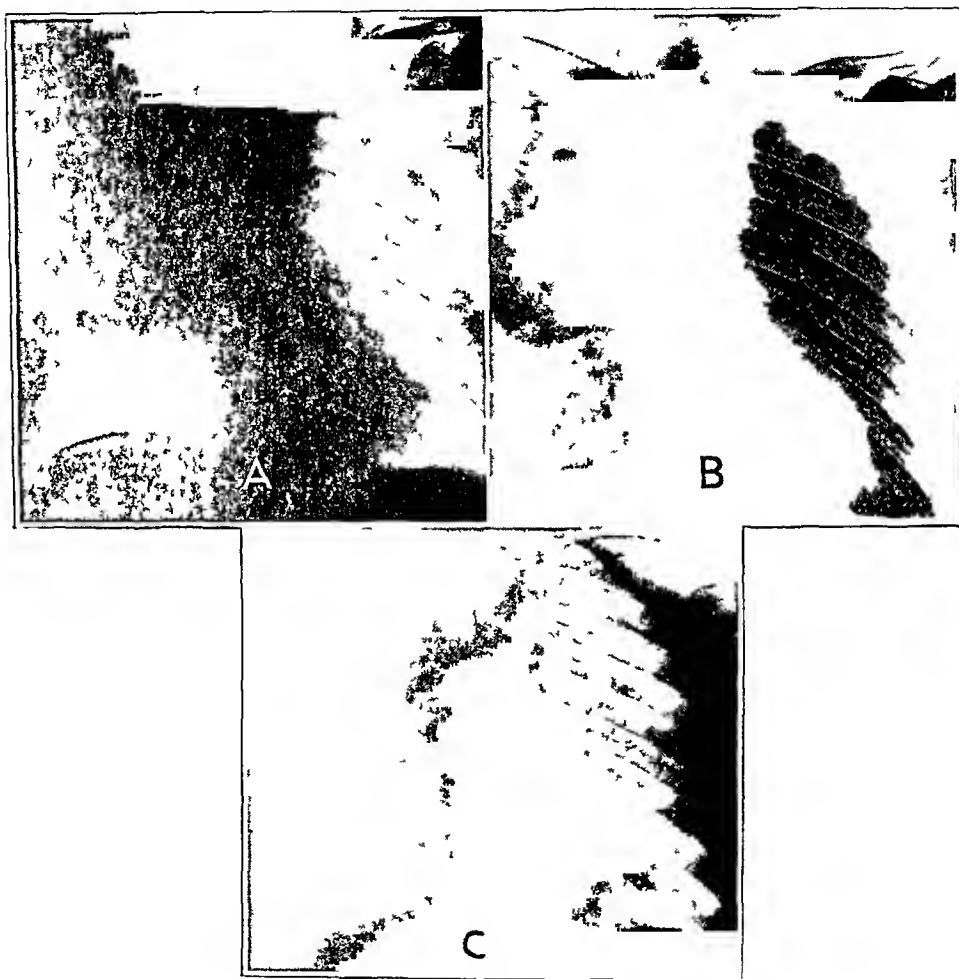


Fig 2 (case 4) —*A* roentgenogram taken on Dec 23, 1932, showing consolidation of the right upper lobe *B*, roentgenogram showing resolving pneumonia in the upper lobe of the right lung on Dec 27, 1932 The irregular rarefaction suggests the formation of cavities *C* on Jan 14, 1933, the lesion involving the right upper lobe was smaller Multiple abscess cavities were present with fluid levels

his drowsy state There was a slight increase in the amount of cough The type of sputum remained as it had been on admission but the amount was smaller

By December 30 the patient appeared much brighter mentally The percussion note over the upper lobe of the right lung was less dull Roentgenographic examination on Jan 5 1933 was reported as follows "The diagnosis is Fried-

lander's pneumonia The area of cavitation found in the previous examination is not as evident at this examination as previously There is still involvement of the entire upper lobe of the right lung, but one obtains the impression that there has been some improvement" On January 10 the entire lobe still remained dull to percussion, both anteriorly and posteriorly After coughing, cavernous breathing was distinctly heard anteriorly, associated with moist rales and whispering pectoriloquy Culture of the sputum on January 14 still showed *B. mucosus-capsulatus* in moderate numbers On January 14 (fig 2C) Dr Pendergrass reported "The lesion involving the upper lobe of the right lung is smaller than at the previous examination There are multiple abscess cavities present with fluid levels The homogeneous density is probably due to the fact that the lesion extends outward and has caused a slight pleural reaction"

On January 23 the temperature had not risen above 99 F for five days The patient was becoming restless and declared that he was able to get up and go home However, at that time there were still definite limitation in respiratory excursion and dulness to percussion over the entire upper lobe of the right lung Auscultation revealed bronchial breath sounds The red cell sedimentation rate on January 25 was markedly accelerated Culture of the sputum on January 24, showed three colonies of *B. mucosus-capsulatus*, a moderate growth of green streptococci and a few organisms of the *Micrococcus catarrhalis* type On January 27 (fig 3A) Dr Pendergrass' roentgen observations were "The diagnosis is Friedlander's pneumonia The lesion has improved slightly since the last examination There are still multiple fluid levels in the upper lobe of the right lung Surrounding these areas there is a homogeneous density, probably due to an atelectatic lung"

The patient was first allowed out of bed on January 24 Although his strength returned rather rapidly, the clinical and roentgenologic signs over the upper lobe of the right lung remained virtually unchanged The sedimentation curve obtained on January 25 and that obtained on February 15 were almost superimposable However, in spite of these facts, it was deemed safe to discharge the patient on February 16

Treatment during this attack of pneumonia consisted entirely of supportive and symptomatic measures No form of specific treatment was used Resort was not made even to postural drainage

After discharge the patient did not return to work He felt well except for shortness of breath on the slightest exertion Some edema of the ankles had been noted, which would disappear by the following morning There was a small amount of sputum, which was never blood tinged

The patient was readmitted to the hospital on May 8, particularly for a survey of the pulmonary lesion The temperature and the pulse and respiratory rates were normal The physical signs in the chest were very much as they had been three months previously Over the upper lobe of the right lung there were limitation in expansion, dulness to percussion and cavernous breath sounds, with bronchophony and whispering pectoriloquy Examination of the blood at that time showed 5,600,000 red cells, 7,000 white cells and 108 per cent hemoglobin (17.9 Gm) per hundred cubic centimeters The differential count showed 67 per cent polymorphonuclear neutrophils, 27 per cent lymphocytes, 5 per cent large mononuclears and 1 per cent eosinophils Of the neutrophils, 36 per cent were of the filament form and 31 per cent were nonfilamented A roentgenogram of the chest made on May 9 (fig 3B) was interpreted as follows "Chronic infection with Friedlander's bacillus is present, involving the upper lobe of the right lung There has been considerable improvement in the appearance of the chest since

the last examination There remains, however, considerable fibrosis involving the upper lobe of the right lung, with evidence of cavitation There is also considerable thickening of the pleura at the extreme apex The trachea and heart are still definitely drawn to the right" Examination of the sputum did not show *B. mucosus-capsulatus*

On Nov 8, 1934, the patient was again admitted to the hospital, complaining of cough and shortness of breath However, there was no sputum There was no pain over any portion of the chest The temperature was 98 F, the pulse rate 66 and the respiratory rate 20 The blood pressure was 166 systolic and 88 diastolic There was no cyanosis The trachea was freely movable but was distinctly displaced to the right There were still definite physical signs of involve-

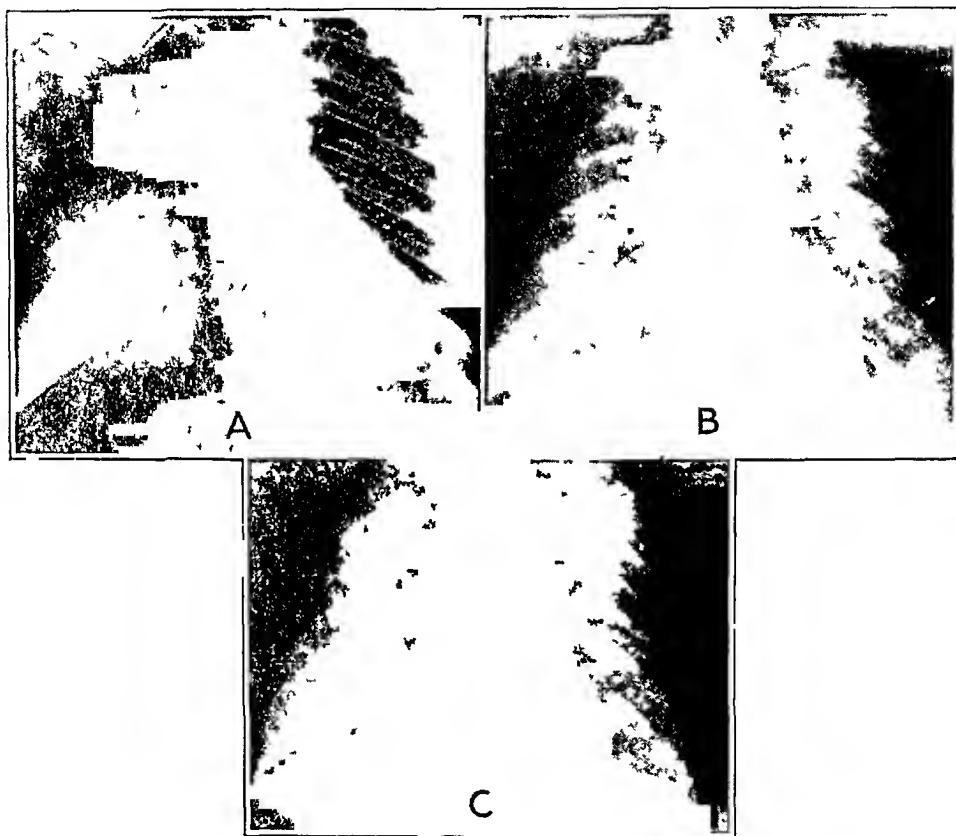


Fig 3 (case 4)—*A*, roentgenogram taken on Jan 27, 1933, showing slight improvement There were still multiple fluid levels in the upper lobe of the right lung *B*, roentgenogram taken on May 9, 1933, showing considerable improvement There still remained, however, considerable fibrosis involving the upper lobe of the right lung, with evidence of cavitation The trachea and heart were definitely drawn to the right *C*, On Nov 9, 1934, there were multiple annular shadows which simulated cavities having thin walls There was some thickening of the apical pleura, with displacement of the trachea toward the right

ment over the upper lobe of the right lung, consisting of a slight decrease in expiratory excursion and an increase in tactile fremitus, with distinct impairment in the percussion note The breath sounds were bronchial in character Egophony and whispering pectoriloquy were present in the apex of the right axilla After the patient coughed, an occasional râle could be heard The remainder of the chest was clear on physical examination

Hematologic examination on Nov 11, 1934, showed 4,500,000 red cells, 7,000 leukocytes and 85 per cent hemoglobin, 68 per cent of the leukocytes were polymorphonuclears

The erythrocyte sedimentation rate was much slower than it had been on the two previous occasions. Because there was no sputum, material from the throat was examined by smear and culture. The smear showed an occasional polymorphonuclear leukocyte, gram-positive cocci and short chains and occasional gram-negative rod forms. Culture showed a predominance of pneumococci, a moderate number of nonhemolytic streptococci, an occasional organism identified as *Micrococcus catarrhalis* and an occasional hemolytic streptococcus. No organisms of the mucosus group were seen.

The report of examination of the chest on Nov 9, 1934 (fig 3 C), by Dr Pendergrass, was as follows: "There are multiple annular shadows, which simulate cavities, and which may be thin-walled cavities. There is some thickening of the apical pleura, with displacement of the trachea toward the right. I can find no evidence of active disease at this time."

When this paper was written (June 15, 1935) the patient was working at manual labor. His only complaint was dyspnea on exertion.

The essential features of these four cases are summarized in the table.

*Cases of Chronic Pulmonary Infection Due to the Friedlander Bacillus*

Case No	Age	Sex	Race	Location of Lesion	Type of Anatomic Distribution	Complications	Ultimate Result
1 J A	50	M	Italian	Upper, middle and lower lobes of right lung	Lobular	Formation of multiple abscesses throughout the right lung	Living 7 years later, no respiratory symptoms
2 M P	50	F	English	Upper and lower lobes of left lung	Lobar	Formation of large abscess in upper lobe of left lung	Death from venous thrombosis and sepsis two years after the attack of pneumonia following an attack of acute sore throat, apparently unrelated to earlier infection
3 T M	43	M	American Negro	Upper lobe of right lung, lower and upper lobes of left lung	Lobar	Formation of multiple abscesses in upper lobe of left lung	Unknown at the time of writing
4 J J	63	M	Italian	Upper lobe of right lung	Lobar	Formation of multiple abscesses in upper lobe of right lung	Working as a laborer two years later, marked dyspnea on exertion

#### COMMENT

The organism that was isolated from the sputum of the first three patients and from the blood and sputum of the fourth was a gram-negative nonmotile bacillus, with a large, easily stained capsule. It formed large, moist, semitranslucent mucinous colonies when cultured on blood agar. It produced acid and gas in dextrose and usually in saccharose. It caused little or no fermentation of lactose, it did not produce indole, it gave rise to slight acidity in milk, without coagulation,



it did not liquefy gelatin. Thus, it would be considered to be one of the S variants in Julianelle's<sup>4</sup> classification. He obtained from pure capsulated S strains noncapsulated R strains by cultivation in broth containing 10 per cent of homologous immune serum. Recent work<sup>5</sup> has shown the importance of the capsule in determining the virulence of a strain and that cultures of the same species show great differences, depending on their age, the method of cultivation and other factors which affect the formation of capsules.

The literature contains ample reference to the acute, rapidly fatal form of pneumonia caused by this organism. Recently Bensley<sup>6</sup> reported the clinical and pathologic findings in a 42 year old man who died on the sixth day of the attack. Friemmel, Henrichsen and Sweany<sup>7</sup> reported clinical and pathologic data on the case of a 49 year old man who died twenty-six hours after the onset of the acute pulmonary infection. Olcott<sup>8</sup> described the lesions in six patients who died in New York. In five of his patients culture of blood obtained at autopsy revealed the Friedlander bacillus, in the sixth the organism was cultured from the lung. In all six cases the course was acute, death occurring in from two to ten days after the onset of acute symptoms. All the patients were men between 38 and 55 years of age, four were white and two were Negroes. Three had a definite history of alcoholism, and three had a history of chronic infection of the upper respiratory tract. In four instances there was pneumonia of lobar distribution, in one, pneumonia of the lobular type, and in one, lobar distribution in one lobe and lobular in another. In five instances a typically mucinous appearance was seen on cross-section. The pulmonary alveolar walls were more or less injured in all.

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4 Julianelle, L. A. (a) A Biological Classification of *Encapsulatus Pneumoniae* (Friedlander's Bacillus), *J. Exper. Med.* **44** 113, 1926, (b) Immunological Relationships of Encapsulated and Capsule-Free Strains of *Encapsulatus Pneumoniae* (Friedlander's Bacillus), *ibid.* **44** 683, 1926, (c) Immunological Relationships of Cell Constituents of *Encapsulatus Pneumoniae* (Friedlander's Bacillus), *ibid.* **44** 735, 1926.

5 (a) Bensted, H. J., and others. A System of Bacteriology in Relation to Medicine, Medical Research Council, London, His Majesty's Stationery Office, 1929, vol. 4, p. 286. (b) Kiewe, H. Epidemiologische und biologische Studien über den *B. pneumoniae* Friedländer und verwandte Arten, *Zentralbl. f. Bakt.* (Abt. 1) **116** 92, 1930. (c) Neuber, E. Über spezifische Schutzstoffe des mit Kapselbakterien (*Sklerom-Ozaena-Friedländer-Bacillen*) infizierten Organismus, *Arch. f. Dermat. u. Syph.* **170** 154, 1934.

6 Bensley, E. H. A Case of Friedlander's Pneumonia, *Canad. M. A. J.* **26** 681, 1932.

7 Friemmel, F., Henrichsen, K. J., and Sweany, H. C. Pneumonia from Friedlander's Bacillus, *Ann. Int. Med.* **5** 886, 1932.

8 Olcott, C. T. Pneumonia Due to Friedlander's Bacillus, *Arch. Path.* **16** 471 (Oct.) 1933.

Most writers have stressed the rarity of the Friedlander bacillus as the causative agent of pneumonia in infancy and early childhood. Comba<sup>9</sup> reported such a case in 1896, the organism being obtained in pure culture from the blood of the heart and from exudate from the lungs. In 1915 Dunn and Hammond<sup>10</sup> reported an instance of pneumonia with recovery in a 14½ month old boy. The condition clinically presented the features of lobar pneumonia, first of the lower lobe of the left lung with crisis, and then a reinfection of the upper lobe of that lung. While thoracentesis was being attempted, the exploring needle entered the underlying lung, no fluid being obtained from the pleural cavity. Bacteriologic examination of the contents of the lumen of the exploring needle revealed a pure culture of a gram-negative encapsulated bacillus. The organism corresponded in morphologic structure and in all cultural characteristics to *B. mucosus-capsulatus*. This case is apparently the first in which recovery was reported in America from pneumonia due to the Friedlander bacillus.

Khiewe<sup>5b</sup> reported from Germany an epidemic of pneumonia due to the Friedlander bacillus in a home caring for one hundred and thirty children. Two children died. *B. mucosus-capsulatus* seemed to be the sole etiologic agent for the fatal and nonfatal pulmonary lesions. The larger epidemic in Germany, reported by Zander<sup>11</sup> in 1919, has been referred to previously.

Ferguson and Tower<sup>12</sup> in 1933 described pneumonia due to the Friedlander bacillus in twins 7 months old, a girl and a boy. The girl contracted the disease first and died on the eighth day. The boy became ill two days after the onset of the illness in his sister, but he completely recovered after thirty-two days' hospitalization.

Already the literature reveals the appreciation that the chronic sequelae of the acute pneumonic process may strongly suggest, clinically and roentgenographically, chronic pulmonary tuberculosis. From this standpoint the case of Westermarck<sup>13</sup> is of particular interest. Brulé, Huguenin, and Gilbert-Dreyfus<sup>14</sup> reported the clinical course, and

9 Comba. *Friedlander's Pneumonie-Mikrokokkus*, *Jahresb u d Fortschr v d Path Microorg* **12** 101, 1896.

10 Dunn, C H, and Hammond, J. A Case of Friedlander's Pneumonia with Recovery, *Interstate M J* **22** 1133, 1915.

11 Zander, A. Ausgedehnte Endemie von Lungenentzündungen durch Infektion mit Friedlanderschen Pneumobazillen unter Zivilarbeitern, *Deutsche med Wchnschr* **45** 1180, 1919.

12 Ferguson, J A, and Tower, A A. Pneumonia in Infants Due to *Bacillus Mucosus-Capsulatus*, *Am J Dis Child* **46** 59 (July) 1933.

13 Westermarck, N. Ein Tuberkulose vortauschender Fall von Friedlander's Pneumonie mit lange sich hinziehendem Verlauf, *Acta radiol* **7** 626, 1926.

14 Brulé, M, Huguenin, R, and Gilbert-Dreyfus. Pneumopathie chronique a bacilles de Friedlander, *Bull et mem Soc méd d hôp de Paris* **51** 1370, 1927.

Brulé, Huguenin and Foulon<sup>15</sup> reported the pathologic observations, of a chronic pulmonary infection due to the Friedlander bacillus in a woman aged 34. Her illness extended over nine years. A vaccine prepared from the Friedlander bacillus apparently produced some temporary benefit.

Schlapper<sup>16</sup> described the illness of a woman aged 30, which extended over two years. Permission for autopsy could not be obtained. This case is of particular interest because the culture of the Friedlander bacillus obtained from the sputum, contrary to what usually occurs, was overgrown by pneumococci, staphylococci and streptococci. Schlapper concluded that in his case a strain of the Friedlander bacillus less virulent than that usually encountered had been the causative agent. Sweany, Stadnichenko, and Henrichsen<sup>17</sup> in 1931 described the clinical and bacteriologic observations in a chronic pulmonary infection with the Friedlander bacillus fatal after twenty-eight months. The organism differed from that ordinarily described in that it grew as well or better anaerobically as aerobically, it grew poorly on potato medium, it fermented lactose, producing acid and gas, and it produced coagulation in milk. The clinical aspects closely simulated chronic pulmonary tuberculosis, differing from it only in the general appearance of the patient, the irregularity in temperature and the obscure physical observations. The roentgen observations resembled those noted in chronic pulmonary tuberculosis. Toward the end of this patient's illness the odor of the sputum became increasingly offensive. My associates and I have not encountered this feature in any of our four cases.

Gerhartz,<sup>18</sup> in 1933, reported eight cases in which the patient survived the acute stage of the disease. Five patients were men, aged, respectively, 56, 72, 69, 64 and 34, three were women, aged 59, 28 and 30. One of these patients, a man aged 69, died three months after the onset of the illness. In addition to containing the Friedlander bacillus, the sputum was reported to contain pneumococci and numerous spirilla. Two other patients had mixed infections. Two patients, men aged 56 and 34, had an antecedent fibrous pulmonary tuberculosis. There was activation of the tuberculosis by the pneumonic process. One patient, a woman aged 59, evidently contracted the disease from her brother, aged 69, with whom she lived. Gerhartz' eighth patient, a nurse aged

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15 Brulé, M., Huguenin, R., and Foulon, P. Etude anatomo-clinique d'une pneumopathie chronique due au bacille de Friedlander, *Ann d'anat path* **4** 889, 1927.

16 Schlapper, K. Ueber Friedlander-Pneumonien, *Beitr z Klin d Tuberk* **78** 741, 1931.

17 Sweany, H. C., Stadnichenko, A., and Henrichsen, K. J. Multiple Pulmonary Abscesses Simulating Tuberculosis, *Arch Int Med* **47** 565 (April) 1931.

18 Gerhartz, H. Friedlander-Pneumonie, *Med Klin* **27** 147, 1933.

30, presumably contracted the disease from the sixth patient, a 34 year old man. Her pneumonia was complicated by an infection of the urinary tract, both the Friedlander bacillus and the colon bacillus being cultured from the urine <sup>4b</sup>. In the reports of these cases no mention was made of studies of blood cultures.

The first case reported in the literature in which the Friedlander bacillus was cultured from the sputum and from the blood during life seems to be that of Phillipi <sup>19</sup>. The patient was described as "a robust old man." Death occurred shortly after his admission to the hospital. Phillipi felt that no similar case had previously been reported.

Apelt <sup>20</sup> reported ten cases in patients aged, respectively, 42, 46, 51, 50, 30, 53, 50, 38, 74 and 44. All the patients were men except two. The condition ended fatally in all the cases except case 4. In cases 1 and 2 the Friedlander bacillus was cultured from both the sputum and the blood. The one patient who recovered had four sterile blood cultures. From the sputum of this patient, in addition to the Friedlander bacillus, staphylococci were cultured. Apelt concluded that, to his knowledge, case 4 in his series was the first case of pneumonia bacillus due to the Friedlander in which the patient had recovered.

In America the case of Dunn and Hammond <sup>10</sup> seems to be the first reported instance of recovery. This case is also of interest as one of the early cases in which bacteriologic diagnosis was possible by means of lung puncture. However, apparently it was not done purposely, as has been suggested by Horder <sup>21</sup>.

#### DIAGNOSIS

The leukocyte counts of our first three patients were all above normal, though they were less than those seen in the usual case of pneumococcic lobar pneumonia. The actual counts are given in a former paper <sup>1c</sup>. The temperature, pulse rate, respiratory rate and leukocyte curves in case 4 are given in figure 4. At *A* the Friedlander bacillus was isolated from the blood stream. At *B* the blood culture was sterile. In four of Olcott's <sup>8</sup> cases, the blood counts showed less than 7,000 leukocytes, in one of these the number was less than 2,000, with 24 per cent large mononuclears.

During the acute stage all our patients had bloody mucoid sputum, not particularly malodorous, in fairly large amounts. From this sputum we succeeded repeatedly in culturing the Friedlander bacillus in pure culture or as the predominant organism. The organism obtained from

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19 Phillipi, E. Ein Fall von kruppöser Pneumonie und Sepsis, hervorgerufen durch den Pneumobazillus Friedlander, München med Wchnschr **49** 1884, 1902.

20 Apelt, F. Ueber die durch den Bacillus Pneumoniae Friedlander hervorgerufene Pneumonie, München med Wchnschr **55** 833, 1908.

21 Horder, T. Lung Puncture. A New Application of Clinical Pathology, Lancet **2** 1345, 1909.

the blood in case 4 seemed to be biologically identical with that isolated simultaneously from the sputum. The patient in case 1, who has been under observation for over seven years, and the patient in case 4, who has been under observation for over two years, raise no sputum at the time of writing. Culture of material from their throats reveals no Friedlander bacilli. In none of our patients, either in the acute or in the chronic stage, have we resorted to puncture of the lung<sup>21</sup> as an aid in diagnosis. Repeated examinations have never disclosed tubercle bacilli in the sputum of any of the patients.

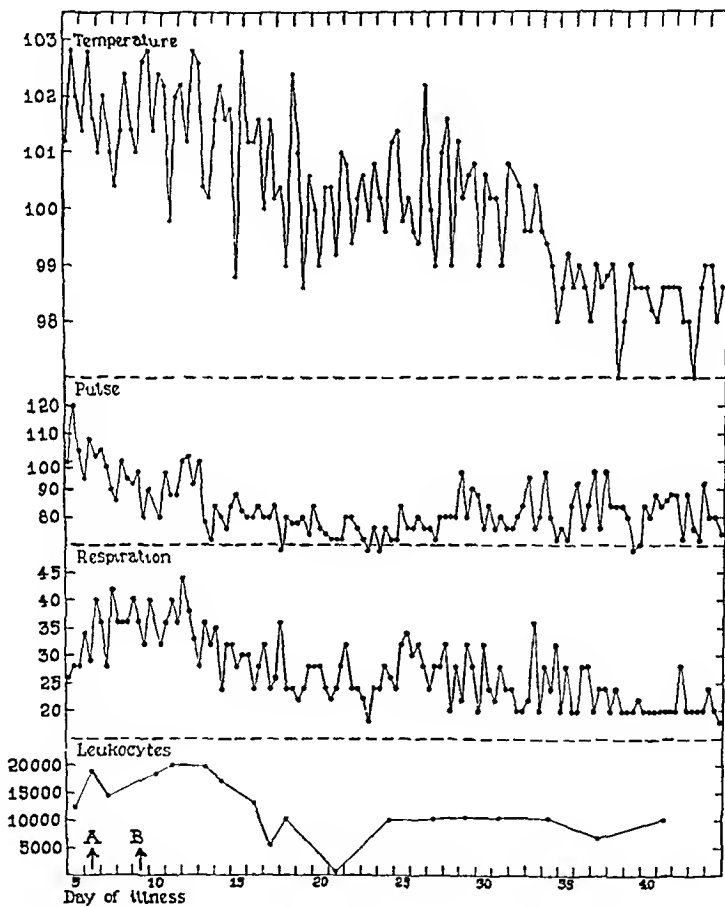


Fig 4 (case 4) —At A, B *mucosus-capsulatus* was recovered in pure culture from the blood stream. At B, the blood culture was sterile.

All our patients at some stage have shown formation of the cavities (table 1). Roentgenologically, it has appeared that the cavity walls are thin. This is in keeping with the observations of Westermarck<sup>13</sup> and of Gerhartz<sup>18</sup>. "Large thick-walled cavities do not suggest Friedlander pneumonia." However, in reporting their case, Sweany, Stadnichenko and Henrichsen<sup>17</sup> stated that "the roentgen observations resembled those noted in chronic pulmonary tuberculosis."

## TREATMENT

The treatment of our patients consisted of comfortable rest in bed. Resort was not made even to postural drainage. Several patients whose cases are reported in the literature have had surgical drainage of the pulmonary lesion. In Apelt's <sup>20</sup> case in which the patient recovered he apparently was well eighteen days after operation. Schlapper's <sup>16</sup> patient died shortly after operation.

The use of an autogenous vaccine by Brule, Huguenin and Gilbert-Dreyfus <sup>14</sup> has been referred to previously. The preparation of a bacteriophage by Caublot <sup>22</sup> and the immunologic studies of Neuber <sup>5c</sup> concerning specific protective substances following infection with the Friedlander bacillus may in the future prove therapeutically useful.

## SUMMARY

Follow-up data are presented concerning three previously reported cases of recovery from pneumonia due to the Friedlander bacillus. One of these patients was still living over seven and one-half years after the attack of pneumonia. One patient died of an apparently unrelated infection two years after the attack of pneumonia. The third patient we have been unable to locate.

A fourth case of recovery is reported. In this case the Friedlander bacillus was isolated from both the sputum and the blood during the acute stage of the pneumonia. This patient is now doing manual labor, over two and one-half years after the attack of pneumonia. At the site of the original pneumonic lesion there are still marked clinical and roentgenologic signs.

The end-result of pneumonia due to the Friedlander bacillus, both clinically and roentgenologically, almost completely simulates chronic pulmonary tuberculosis in that it produces cavitation, displacement of the trachea, elevation of the domes of the diaphragm and elevation of the hili of the lungs.

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<sup>22</sup> Caublot, P. Le bacteriophage du pneumobacille de Friedlander, *Compt rend Soc de biol* **90** 622, 1924.

# CONVULSIVE SEIZURES IN ADULT LIFE

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One of the most startling and to the laity most terrifying symptoms of disease is a fit. Particularly is this true when the afflicted person is an adult, for convulsive attacks in children are not infrequently observed even by the layman. When an adult who has apparently been in perfect health has an epileptiform attack it creates such a vivid impression on the witnesses that a physician is consulted at once. The latter has not an easy task, for to ferret out the etiologic agent producing an epileptic attack in an adult who has never previously had a convulsive seizure demands the keenest clinical acumen. While idiopathic epilepsy is common in childhood, it becomes rarer as age increases, and, as Oppenheim<sup>1</sup> stated, "We must always be on our guard when the epilepsy develops during adult life."

Epilepsy is merely a symptom complex or, as Foerster<sup>2</sup> said, a special form of reaction of the central nervous system. In order to explain why certain persons with organic lesions of the brain have epileptic seizures while others, with just as severe lesions, do not, some authorities have hypothesized a special "x" factor, or convulsive capacity, for persons having seizures. It seems simpler, however, to assume that any one's nervous system might react with a seizure were the stimulus sufficiently intense. In other words, the convulsive capacity is a pathophysiologic reaction of the central nervous system, the threshold of stimulation to which varies. In the person with idiopathic epilepsy the threshold is low, and a slight upset in the regulation of the normal bodily activities is sufficient to cause a convulsion.

A convulsion may be produced either by increasing the intensity of stimulation until it reaches the convulsive threshold or by lowering the threshold to a level at which a lesser stimulus is effective. The first method is illustrated when galvanic stimulation of the cortex produces

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Read before the combined meeting of the medical societies of Johnson, Iowa, Cedar, Muscatine, Louisa and Washington counties at the University of Iowa, May 1, 1935.

1 Oppenheim, H. Textbook of Nervous Diseases, Edinburgh, The Darien Press, 1911, vol 2, p 1424.

2 Foerster, O. Die Pathogenese des epileptischen Krampfanfalles, Deutsche Ztschr f Nervenhe 94 15, 1926.

fits, and the second, when hyperventilation produces an alkalosis which increases the irritability of the central nervous system. In some cases the factors that cause these changes are known, and the condition is spoken of as symptomatic epilepsy, in other cases, in which the disturbing factor is unknown, the term idiopathic epilepsy is used.

In this paper the factors responsible for convulsions in the adult will be discussed. A series of a hundred patients with epilepsy beginning in adult life, admitted to the service of Dr. Clarence E. Van Epps at the University Hospitals, will be analyzed. Besides the routine physical and laboratory examination, a complete neurologic study, including an examination of the cerebrospinal fluid, roentgenographic examination of the skull and in many of the cases of idiopathic epilepsy encephalography, was made to determine any possible organic etiology for the attacks. No cases of petit mal alone or localized twitching were included. All the patients had had major attacks, although four had not had a clonic convulsion and their condition was classified as major epilepsy sine agitatione.

TABLE 1—*The Age Incidence and Etiology of Epilepsy Occurring for the First Time in Adult Life in One Hundred Patients*

Etiologic Factor	Age					Total
	20-29	30-39	40-49	50-59	60	
Idiopathic	21	17	9	0	0	47
Tumor of the brain	4	5	5	2	0	16
Neurosyphilis	4	5	5	1	0	15
Hypertension and arteriosclerosis	0	1	3	5	5	14
Trauma	3	0	1	0	0	4
Miscellaneous	1	2	1	0	0	4
Total	33	30	24	8	5	100

Table 1 shows the final diagnosis in the cases and the age incidence of the types of epilepsy. It is obvious from a perusal of this table that while idiopathic epilepsy is the most common type occurring in adult life it becomes rarer as age increases and after 40 constitutes only 21 per cent of all cases. The highest incidence of epilepsy due to syphilis of the central nervous system or to tumor of the brain occurs at the age when those diseases have their greatest frequency. As would be expected, epileptiform convulsions as a manifestation of hypertension and cerebral arteriosclerosis occur in late adult life.

If the types are analyzed to determine the total number and frequency of attacks (table 2), it at once becomes evident that idiopathic epilepsy has greater frequency and causes many more attacks than epilepsy with demonstrable intracerebral pathologic changes. It is also apparent that a considerable number of the patients with organic lesions had only one or two convulsions. The difference between the types may be due to several factors. In the first place, other evidence of cerebral dysfunc-



tion causes the patient with an organic lesion to report to the physician before many attacks have occurred. In many cases, however, only one or two attacks occur over a period of several years, so it must be assumed that the symptomatic variety does not have the periodicity which is characteristic of idiopathic epilepsy. It is interesting to note that the incidence of petit mal is much higher in idiopathic than in symptomatic epilepsy.

A consideration of the pathologic conditions which manifest themselves at times by epileptic attacks<sup>3</sup> will be of assistance in a further analysis of the cases under consideration.

TABLE 2—*The Frequency and the Total Number of Attacks, According to the Etiology of the Epilepsy*

Etiologic Factor	Number of Attacks			Frequency of Attacks		Type	
	1	2 to 10	Over 10	Less than 1 per Mo	More than 1 per Mo	Minor	Jacksonian
Idiopathic	0	7	40	19	28	20	3
Tumor of the brain	4	10	2	12	4	3	2
Neurosyphilis	1	9	5	10	5	3	
Hypertension and cerebral arteriosclerosis	1	9	4	13	1	1	2
Trauma	0	0	4	4	0		1
Miscellaneous	0	3	1	4	0		

#### TUMOR OF THE BRAIN

Convulsive seizures are not infrequent manifestations of cerebral neoplasm. Sargent<sup>4</sup> reported an incidence of convulsions of 30.9 per cent in a series of 270 patients. Parker<sup>5</sup> in a series of 313 patients with cerebral tumor found that 67 (21.4 per cent) had major epileptic convulsions. Dowman and Smith<sup>6</sup> found that seizures occurred in 39 per cent of 100 cases of intracranial growth. In a statistical survey of Bailey's cases from the University of Chicago, Ley and Walker<sup>7</sup> found that 25.7 per cent of the patients suffering from tumor of the brain had generalized convulsions.

3 (a) Brock, Samuel. The Convulsive State, *Arch Neurol & Psychiat* **20** 420 (Aug.) 1928. (b) Cobb, Stanley. Causes of Epilepsy, *ibid* **27** 1245 (May) 1932. (c) Lennox, W. G., and Cobb, Stanley. Epilepsy, Harvard Medicine Monographs, Baltimore, Williams & Wilkins Company, 1928, p. 197.

4 Sargent, Percy. Some Observations on Epilepsy, *Brain* **44** 312, 1921.

5 Parker, H. L. Epileptiform Convulsions, *Arch Neurol & Psychiat* **23** 1032 (May) 1932.

6 Dowman, E. C., and Smith, W. A. Intracranial Tumors, *Arch Neurol & Psychiat* **20** 1312 (Dec.) 1928.

7 Ley, A., and Walker, A. Earl. Statistical Review of Two Hundred and Thirty Intracranial Tumors, *Rev de cir de Barcelona* **10** 197 (Oct.) 1935.

The frequency of epileptic manifestations varies considerably with the site and the type of intracranial neoplasm. A tumor of the temporal, parietal or frontal lobe produces seizures more frequently than one in another region (Gibbs<sup>8</sup> and Groff<sup>9</sup>). It has been stated that glioma is more prone to cause epileptic attacks than meningioma, but Groff found that 30.9 per cent of patients with meningioma had fits—an incidence certainly as high as that in all cases of tumor of the brain or all cases of glioma. The truth of Groff's statement is more apparent than real, for while approximately one third of all gliomas occur in the posterior fossa, less than 10 per cent of meningiomas (Groff<sup>9</sup> and Elsberg<sup>10</sup>) occur there. Since it is well recognized that a lesion of the posterior fossa rarely causes epileptic attacks, a more accurate statistical report would be based on cases of supratentorial tumor. From such a report it would be obvious that the incidence of epilepsy with glioma is somewhat higher than that with meningioma.

That a convulsion may be the initial symptom of cerebral tumor is well known, and the symptomatology in approximately 15 per cent of all cases of tumor of the brain is ushered in by an epileptic seizure (Parker<sup>5</sup> gave the percentage as 12.1, Dowman and Smith,<sup>6</sup> as 15, and Ley and Walker,<sup>7</sup> as 12.9). Appreciation of this fact is of utmost importance if the rather gloomy outlook for the treatment of tumor of the brain is to be improved. The early recognition of an intracranial growth is essential if surgical therapy is to be effective, for by the time the diagnosis becomes evident to any tyro, the lesion is frequently so large that it cannot be removed without leaving the patient in a socially, if not an absolutely, helpless condition. At the time of the first convulsion many patients have sufficient neurologic abnormalities to make the correct diagnosis possible. There are, however, a certain number in whom no abnormalities can be found (in the present series, four of sixteen patients), and one must rely on accessory aids. Roentgenograms of the skull may show erosion or hyperostosis of the cranium or calcification within the neoplasm and thus make diagnosis possible. Such abnormalities unfortunately do not often accompany cerebral tumor. If no further examination were made, the diagnosis would be idiopathic epilepsy, and not until the onset of more ominous symptoms would the true condition be suspected.

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8 Gibbs, F. A. Frequency with Which Tumors in Various Parts of the Brain Produce Certain Symptoms, *Arch Neurol & Psychiat* **28** 969 (Nov) 1932

9 Groff, Robert A. The Meningioma as a Cause of Epilepsy, *Ann Surg* **101** 167, 1935

10 Elsberg, Charles A. The Parasagittal Meningeal Fibroblastomas, *Bull Neurol Inst New York* **1** 389, 1931

## NEUROSYPHILIS

Convulsive attacks may occur as a result of involvement of the central nervous system in either the secondary or the tertiary stage of syphilis. Early in the secondary stage there is frequently a mild meningeal reaction, usually manifested only by headache but occasionally giving rise to a generalized convulsion. The more acute syphilitic meningitis, particularly that occurring over the vertex, not infrequently gives rise to fits. In the late secondary stage the meningovascular and cerebral types of syphilis occasionally manifest themselves by epileptic attacks. Tertiary lesions, particularly gumma and dementia paralytica, frequently cause seizures. The incidence of attacks in dementia paralytica has been estimated variously by different authors. Kraepelin<sup>11</sup> has expressed the belief that they occur in from 30 to 90 per cent of all cases. In some of the cases he described, however, the patient had only minor spells without a true loss of consciousness and without a clonic convulsion. Fournier<sup>12</sup> stated that convulsive seizures which appear for the first time in a patient when he is from 30 to 40 and apparently in good health are eight or nine times out of ten of syphilitic origin. This estimate is undoubtedly far too high, but it serves to emphasize the importance of *Spirochaeta pallida* as an etiologic factor in epilepsy beginning in adult life.

There are several suggestive distinguishing points between idiopathic epilepsy and epilepsy due to neurosyphilis. Nonne<sup>13</sup> observed that the intelligence suffers much less in the latter than in true epilepsy and that long remissions are characteristic. The second point is well illustrated in the present series, in which ten of the fifteen patients had less than five attacks, although the majority had had attacks over a longer period than one year.

In many cases epilepsy caused by neurosyphilis can be diagnosed clinically. A routine psychiatric and neurologic examination frequently shows sufficient abnormality to lead one to suspect a syphilitic involvement of the central nervous system even in the absence of a history of syphilitic infection. With the routine use of the Wassermann and the Kahn test of the blood the diagnosis is readily confirmed, for almost all patients with early secondary syphilis, gumma or dementia paralytica have a positive Wassermann reaction. As mentioned, these are the patients in whom convulsions are most common. In epilepsy due to

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11 Kraepelin, E. *General Paresis*, translated by J. W. Moore, Nervous and Mental Disease Monograph 14, New York, Nervous and Mental Disease Publishing Company, 1913, p. 200.

12 Fournier, A. *La syphilis du cerveau*, Paris, G. Masson, 1879, p. 654.

13 Nonne, Max. *Syphilis and the Nervous System for Practitioners, Neurologists and Syphilologists*, translated by Charles R. Ball, ed. 2, Philadelphia, J. B. Lippincott Company, 1916, vol. 24, p. 450.

other types of syphilitic involvement of the central nervous system—meningovascular syphilis, cerebral syphilis, etc—in which the Wassermann reaction is not so frequently positive—the history, neurologic findings and course of the disease usually point to the correct diagnosis. Fourteen of the fifteen patients in the present series who had epileptiform attacks due to neurosyphilis, had markedly positive Wassermann and Kahn reactions of the blood. Thirteen had a Wassermann and a Kahn reaction of 4 +, and the fourteenth had a Wassermann reaction of 1 +, and a Kahn reaction of 3 +. The fifteenth patient died shortly after admission in status epilepticus, and a Wassermann test was not made.

#### HYPERTENSION AND ARTERIOSCLEROSIS

A great deal has been written on the rôle of hypertension and arteriosclerosis in the production of senile epilepsy, or *epilepsia tarda*.<sup>14</sup> In 1859 Kussmaul and Tenner<sup>15</sup> produced convulsions by jugular compression and severe bleeding and considered cerebral anemia one of the most important factors in the production of epileptic attacks. Their findings have been verified many times (Flesch<sup>16</sup> and Naunyn<sup>17</sup>), and cerebral anemia is still considered an important, if not the prime, factor in the production of seizures, particularly as several observers have seen the blanching of the cerebral cortex at operation just before a fit. The narrowing of the lumen of a vessel caused by arteriosclerosis undoubtedly is very important in producing cerebral anemia, but the anemia is produced slowly and so does not give rise to the same symptoms as does a rapidly produced anemia.<sup>18</sup> The theory most favored to explain the production of the cerebral anemia that is believed to occur when a fit is initiated is based on vasoconstriction. With the demon-

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14 (a) Cross, Ernest S. The Significance of Epileptiform Seizures Originating in Adult Life, *M. Clin. North America* **16** 1227 (March) 1933. (b) Matorne, O. Senile Epilepsy, with the Report of Four Cases, *Internat. Clin.* **3** 174, 1928. (c) Osborne, O. T. Epilepsy Late in Life, *Ann. Int. Med.* **1** 841, 1928. (d) Redwood, Frank H. Senile Epilepsy (*Epilepsia Tarda*), *Virginia M. Monthly* **55** 804, 1929. (e) Savill, Thomas D. Senile Epilepsy and the Vertiginous Attacks Which Supervene for the First Time in Advanced Life, Illustrated by a Case of Cardio-Arterial Hypertrophy, *Lancet* **2** 131, 1909. (f) Sympton, E. Mansel. Remarks on Senile Epilepsy, *Brit. M. J.* **1** 1069, 1894.

15 Kussmaul, A., and Tenner, A. *Epileptiform Convulsions Caused by Profuse Bleeding and Also True Epilepsy*, translated by E. Bronner, London, New Sydenham Society, 1859.

16 Flesch, J. Die Auslösung von Anfällen durch Karotiden Kompression, *Wien klin. Wchnschr.* **28** 1422, 1915.

17 Naunyn, B. Ueber senile Epilepsie, *Ztschr. f. klin. Med.* **28** 217, 1895.

18 Gildea, E. F., and Cobb, Stanley. The Effects of Anemia on the Cerebral Cortex of the Cat, *Arch. Neurol. & Psychiat.* **23** 876 (May) 1930.

stration of nerve fibers along the cerebral vessels<sup>19</sup> and vasoconstriction by stimulation of cervical sympathetic fibers,<sup>20</sup> the theory has been further emphasized. Lange<sup>21</sup> observed that there is very little vasoconstrictor reaction in sclerosed vessels, and so some other mechanism must be present if arteriosclerosis is an important cause of epilepsy. Krapf,<sup>22</sup> however, pointed out that simple senile changes in the brain and arteriosclerosis cannot be important factors, for epilepsy rarely begins or is present at the age (that is, over 70) at which such changes are most prevalent. He also noted that while arteriosclerosis was a prominent concomitant in a group of patients with late epilepsy, it was not the most common factor either clinically or at autopsy. Increased blood pressure with marked fluctuations was present in 85 per cent of his cases, and he concluded that this was the most important factor. In support of his contention he quoted Lange, who had observed that vascular constriction was more pronounced and more readily produced in a hypertensive than in a normal state. Most American writers (Elliott,<sup>23</sup> Reisman and Fitz-Hugh,<sup>24</sup> and Redwood<sup>14d</sup>) place equal emphasis on hypertension and arteriosclerosis. Oppenheimer and Fishberg,<sup>25</sup> however, expressed the belief that hypertension is the important factor not only in hyperpiesia but also in uremia and lead poisoning.

Only three of the fourteen patients in the series under discussion with hypertension or arteriosclerosis of the brain had definite and marked peripheral arteriosclerosis. Five had evidence of cerebral thrombosis and softening and probably had marked cerebral vascular thickening. Ten had a blood pressure above 150 systolic. If 150 is considered the upper limit of normal, then the most common factor in this group is vascular hypertension. In some cases the vascular instability noted by Krapf<sup>22</sup> was seen.

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19 Penfield, W. Intracerebral Vascular Nerves, *Arch Neurol & Psychiat* **27** 30 (Jan) 1932.

20 Forbes, H. S., and Wolff, H. G. Cerebral Circulation. II. The Vasomotor Control of Cerebral Vessels, *Arch Neurol & Psychiat* **19** 1057 (June) 1928.

21 Lange, F. Die Funktion der Blutstrombahn bei Arteriosklerose, *Deutsches Arch f klin Med* **157** 320, 1927, Die Funktion der Blutstrombahn bei Hypertonie, *ibid* **158** 214, 1928.

22 Krapf, E. Ueber Spatepilepsie, *Arch f Psychiat* **97** 323, 1932.

23 Elliott, Arthur R. Epilepsia Tarda—Convulsive Cerebral Crises in High Blood Pressure and Arteriosclerosis, *M Clin North America* **17** 1469, 1934.

24 Reisman, D., and Fitz-Hugh, J. Epilepsia Tarda, *Ann Int Med* **1** 273, 1927.

25 Oppenheimer, B. S., and Fishberg, A. M. Hypertensive Encephalopathy, *Arch Int Med* **41** 264 (Feb) 1928. Fishberg, A. M. Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1934, p. 668.

## TRAUMA

The great war gave an opportunity for the study of the relation of cerebral injury to epilepsy. The incidence of convulsive seizures following major head injuries has been variously reported, at from 25 per cent (Rawling<sup>26</sup>) to less than 5 per cent (Sargent<sup>4</sup>). Wagstaffe<sup>27</sup> observed that epilepsy was much more frequent after penetrating wounds of the dura than after other head injuries, and as a corollary Turner<sup>28</sup> found marked neurologic defects in many cases. The frequency of post-traumatic epilepsy appears greater the longer the period in which the cases are followed, for many patients do not have fits for from five to fifteen years after a head injury (Stevenson<sup>29</sup>). Wagstaffe and Adie,<sup>30</sup> who studied the immediate effect of head injuries, stated that epileptic attacks occur in only 5 per cent of cases and are due to cerebral contusion, laceration, edema or hemorrhage, subarachnoid, subdural or extradural. The patients are not more likely than other persons to have epilepsy later. Turner<sup>28</sup> found that in twenty-five of thirty-six cases in which the time of the first attack was known it occurred within the first year and in the remainder before the lapse of two and one-half years. He noted that fits tend to occur at longer intervals in post-traumatic epilepsy than in the idiopathic variety. Stevenson<sup>29</sup> stated that mental deterioration is more common in posttraumatic epilepsy.

In the four cases included in this report in which the diagnosis was posttraumatic epilepsy, the epilepsy appears to have had a direct relation to cerebral trauma. In all four the cerebral laceration was visualized at operation. Three patients underwent encephalography, which showed abnormalities. In the fourth case roentgenograms of the skull showed a foreign body within the brain substance. The shortest period between the accident and the first attack was three days and the longest interval one and one-half years. Two patients had their first attack on the fourth day and the forty-fifth day, respectively. One patient included in the group with idiopathic epilepsy might have been placed in the class with posttraumatic seizures. He was a man of 26 who four years before admission had suffered a severe head injury in an automobile accident, which had rendered him unconscious for fourteen hours. After an uneventful convalescence he was well for two and one-half years and

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26 Rawling, L. B. Gunshot Wounds of the Head, *Brit J Surg* **10** 93, 1922

27 Wagstaffe, W. W. The Incidence of Traumatic Epilepsy After Gunshot Wounds of the Head, *Lancet* **2** 861, 1928

28 Turner, W. A. Epilepsy and Gunshot Wounds of the Head, *J Neurol & Psychopath* **3** 309, 1923

29 Stevenson, W. E. Epilepsy and Gunshot Wounds of the Head, *Brain* **54** 214, 1931

30 Wagstaffe, W. W., and Adie, W. J. Notes on a Series of One Hundred and Sixty-One Cases of Gunshot Wounds of the Head Treated at No. 7 General Hospital, May to August 1916, *J Roy Army M Corps* **31** 307, 1918

then began to have grand and petit mal attacks about once a month. Physical and neurologic examination gave negative results, and encephalograms showed merely slight dilatation of the lateral ventricles. It is such cases that are difficult to classify, undoubtedly this patient suffered marked cerebral disturbance at the time of his accident which conceivably was sufficient to initiate his attacks.

#### MISCELLANEOUS CONDITIONS

Numerous conditions, both of the central nervous system and of the somatic organs, may manifest themselves in convulsions. Foerster<sup>2</sup> listed the conditions of the central nervous system which may be accompanied by convulsions as follows: congenital disease of the brain, hereditary degenerative processes, traumatic lesions, presence of tumor, parasites, syphilis, tuberculosis, cerebral abscess, swelling of the brain, meningitis, leptomeningitis, chronic arachnoiditis, juvenile encephalitis, epidemic encephalitis, multiple sclerosis, presenile gliosis, senile cortical degeneration, toxic conditions and disturbances of circulation. Many of these conditions have already been discussed, some are peculiar to childhood and have no place in this article. The conditions in which epilepsy may occur in adult life are as follows:

##### Intracranial pathologic conditions

###### Degenerative

Pick's disease

Alzheimer's disease

###### Inflammatory

###### Meningitis

Acute syphilitic and pyogenic

Chronic granulomatous

Pachymeningitis haemorrhagica interna

###### Encephalitis

###### Chronic

Epidemic

Multiple sclerosis

Syphilitic

###### Acute

Suppurative

Nonsuppurative

Abscess of brain

Sequelae

Parasitic disease hydatid cyst and cysticercosis

Thrombosis of the longitudinal sinus<sup>31</sup>

<sup>31</sup> Grinker, Roy R. *Neurology*, Springfield, Ill., Charles C. Thomas, Publisher, 1934, p. 979.

## Traumatic

Cerebral contusions and lacerations (a) edema, (b) scarring <sup>32</sup>

Subarachnoid hemorrhage

Subdural hematoma

Middle meningeal hemorrhage

Electrocution

## Vascular

Arteriosclerosis and hypertension

Cerebral thrombosis, embolism and hemorrhage

Cerebral vascular spasm

Raynaud's disease

Angioneurotic edema <sup>33</sup>

Cerebral aneurysm

## Neoplastic

Glioma

Meningioma

Metastatic brain tumor

Vascular tumor angioma

Other intracranial neoplasms

## General somatic diseases

Metabolic <sup>34</sup>

Protein sensitization

Intrinsic

Extrinsic

Heat stroke

## Respiratory

Pleural epilepsy

Hyperventilation

Asphyxia from any cause

## Cardiovascular

Hypertension

Subacute bacterial endocarditis

Stokes-Adams' syndrome

Paroxysmal tachycardia

Cardiac decompensation

Disease of carotid sinus

## Alimentary

Constipation (chronic intestinal intoxication)

## Renal uremia

## Endocrine

Thyroid hypothyroidism

Pancreas hypoglycemia, spontaneous and induced

Adrenals hypersecretion

Thymus

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<sup>32</sup> Kenyon, James H Traumatic Epilepsy (with Discussion), *Ann Surg* **64** 731, 1916

<sup>33</sup> Bassoe, P Angioneurotic Edema of the Brain, *M Clin North America* **15** 409 (Sept) 1932 Olharo, T Ueber cerebrale Symptome bei angioneurotischen Odem, *Klin Wchnschr* **12** 1185, 1933

<sup>34</sup> Wirth, O Zur Pathogenese des epileptischen Krampfanfalls Stoff-wechselpathologie, *Ztschr f d ges Neurol u Psychiat* **109** 521, 1927



Parathyroids    hypoparathyroidism

Pituitary

Hyperpituitarism

Hypopituitarism

Gonads

Menstruation

Pregnancy

Menopause

Blood discrasias

Pernicious anemia

Hemorrhage

Intoxication

Bacterial

Botulism

Tetanus

Metabolic

Uremia

Toxemia of pregnancy

Acute yellow atrophy

Extraneous

Water

Alcohol

Cocaine

Camphor

Lead

Arsphenamine

Picrotoxin

Magnesium sulfate

Strychnine

Absinth

Thujone

Caffeme

Ergot

Nicotine

Epinephrine

Psychogenic

The congenital diseases of the brain which cause epileptic seizures, and not all do, usually do so long before the person reaches adult life. The same is true of the heredodegenerative diseases. There are, however, two abiotrophies in which convulsive seizures are not uncommon—Pick's and Alzheimer's disease. In the former, convulsions are not common (Thorpe<sup>35</sup>) and usually occur only in the later stages of the disease, at which time a diagnosis is not difficult. In Alzheimer's disease in which convulsions are more common (Henderson<sup>36</sup>) and occur earlier in the course of the disease, the differential diagnosis is more difficult, and accessory aids may be necessary.

35 Thorpe, F. I. Pick's Disease (Circumscribed Senile Atrophy) and Alzheimer's Disease. *J. Ment. Sc.* **78** 302, 1932.

36 Henderson, D. K. Alzheimer's Disease, *J. Ment. Sc.* **76** 646, 1930.

Inflammatory lesions of any part of the central nervous system may give rise to convulsions. A generalized seizure may usher in either acute purulent or chronic meningitis of tuberculous, syphilitic or blastomycetic origin. During the course of such meningitis in children fits are common, but in adults, rarer. In suppurative encephalitis (abscess of the brain) they occur both during the acute stage and, more commonly, as a sequela of the damage to the brain.<sup>37</sup> In the present series there was a case of abscess of the brain—secondary to a pulmonary abscess—in which convulsions were the first symptom.

Epilepsy is rarely seen as a symptom of chronic epidemic encephalitis (von Economo<sup>38</sup>) or of multiple sclerosis<sup>39</sup>.

Parasites within the central nervous system not infrequently produce epileptic seizures, which differ in no way from those occurring in idiopathic epilepsy. The type of parasite most commonly found is the cysticercus, hydatid cyst is rare. The former in the late stages of the disease becomes calcified and may be seen in roentgenograms of the skull. Calcification of the cyst also occurs in muscles and may be demonstrated particularly in the muscles of the thigh by the roentgenologist. Frequently, small nodules are palpable in the skin, a biopsy of these reveals the cysticercosis (Dixon and Smithers<sup>40</sup>).

Toxins and toxic agents not infrequently cause epileptic seizures. In the late stages of botulism fits may occur. One type of ergotism (Barger<sup>41</sup>) is characterized by involvement of the central nervous system, and convulsions are frequent with it. Numerous drugs (Cobb<sup>3b</sup>)—cocaine, strychnine, magnesium sulphate, picrotoxin, absinth, thujone, camphor, caffeine, nicotine, lead and epinephrine—occasionally give rise to convulsive seizures. The relation of alcohol to epilepsy is still debatable, but it is certain that the indulgence in alcohol by persons with epilepsy increases the frequency of attacks. There seems to be sufficient evidence for one to assume that in some cases epilepsy is due to acute<sup>42</sup> or chronic alcoholism.

37 Holden, W. B. Epilepsy Occurring Twenty Years After Operation for Brain Abscess, *S. Clin. North America* **11** 1027, 1931. Adson, Alfred W., and Craig, W. McK. The Surgical Management of Brain Abscess, *Ann. Surg.* **101** 7, 1935.

38 von Economo, C. Encephalitis Lethargica. Its Sequelae and Treatment, translated and adapted by K. O. Newman, London, Oxford University Press, 1931, p. 200.

39 Sachs, B., and Friedman, E. D. General Symptomatology of Multiple Sclerosis, *A. Research Nerv. & Ment. Dis., Proc.* **2** 49, 1921.

40 Dixon, H. B. F., and Smithers, D. W. Epilepsy in Cysticercosis (*Taenia Solium*), *Quart. J. Med.* **3** 603, 1934.

41 Barger, George. Ergot and Ergotism, London, Gurney & Jackson, 1931, p. 279.

42 Yawger, N. S. Alcoholism and Epilepsy, Also So-Called Acute Alcoholic Epilepsy, *Am. J. M. Sc.* **147** 735, 1914.

Almost every known disease is occasionally associated with fits, but unless the concurrence is considerably greater than three in a thousand cases, which is the general rate of occurrence of epilepsy, the association cannot be considered more than coincidental. This fact must be borne in mind when the relation of somatic diseases to the convulsive state is discussed.

Endocrine disturbances have long been blamed for the production of epileptic seizures<sup>43</sup>. When, however, the evidence is critically reviewed, there is found to be little ground for the theory. Dysfunction of the thyroid has been suggested as the basis of seizures, but the occurrence of fits with hyperthyroidism is rare (Lennox and Cobb<sup>3c</sup>), and clinical hypothyroidism is not present with seizures, though 25 per cent of persons with epilepsy have a low rate of oxygen consumption (Lennox and Wright<sup>44</sup>). The relationship of the parathyroids to epilepsy is more interesting. Redlich<sup>45</sup> reviewed a series of cases in which tetany and epilepsy coexisted. He found that after the surgical removal of the parathyroids symptoms of tetany appeared at once but generalized convulsion did not appear for months. Other authors (Curschman<sup>46</sup> and Fischer and Leyser<sup>47</sup>) have suggested a common basis for the two conditions, but there is little evidence for this view. Hyperfunction of the adrenals has been said to be the causative factor in some cases. Convulsions may be produced by the injection of epinephrine but do not appear as symptoms of the adrenal cortical syndrome (Walters, Wilder and Kepler<sup>48</sup>). There is more evidence that the pituitary gland plays a rôle in the causation of fits<sup>49</sup>. Epileptic attacks are not uncommonly a symptom of a pituitary tumor<sup>50</sup>, in Cushing's<sup>51</sup>

43 Limer, J. H. *Endocrine Dyscrasias in the Production of Epileptic States*, New York M. J. **114** 16, 1921.

44 Lennox, W. G., and Wright, L. H. *Studies in Epilepsy VII. The Basal Metabolism*, *Arch Neurol & Psychiat* **20** 764 (Oct) 1928.

45 Redlich, E. *Tetanie und Epilepsie*, *Monatschr f Psychiat u Neurol* **30** 439, 1911.

46 Curschman, H. *Epilepsie und Tetanie*, *Deutsche Ztschr f Nervenhe* **61** 1, 1918.

47 Fischer, H., and Leyser, E. *Epilepsie und Tetanie*, *Monatschr f Psychiat u Neurol* **52** 213, 1922.

48 Walters, W., Wilder, R. M., and Kepler, E. J. *The Suprarenal Cortical Syndrome with Presentation of Ten Cases*, *Ann Surg* **100** 670, 1934.

49 Lowenstein, Paul L. *Relation of the Pituitary Gland to Epilepsy*, *Am J M Sc* **163** 120, 1922. Tucker, B. R. *The Role of the Pituitary Gland in Epilepsy*, *Arch Neurol & Psychiat* **2** 192 (Aug) 1919.

50 Shanahan, W. I. *A Case of Epilepsy Associated with Acromegaly*, *J Nerv & Ment Dis* **34** 289, 1907.

51 Cushing, H. *The Pituitary Gland and Its Disorders*, Philadelphia, J. B. Lippincott Company, 1912, p. 351.

series of ninety-eight cases eighteen patients had fits. Hypopituitary symptoms in persons with epilepsy have been described by many authors, and a certain percentage of patients have been benefited by the administration of the gland substance. Reports of thymic disease and epilepsy are few and usually are of cases in adolescents (Browning<sup>52</sup>). The relationship of the pancreas to convulsive seizures has frequently been discussed. Although the acidosis produced by diabetes tends to inhibit epileptic attacks, seizures do occasionally occur in patients suffering from diabetes. The phenomenon of hyperinsulinism, both spontaneous and induced, is frequently associated with fits and other epileptic states (Wilder<sup>53</sup>).

The relationship of the gonads, particularly in women, to epilepsy has been the subject of much controversy. The occurrence of epileptic attacks at menstruation<sup>54</sup> or during pregnancy is well known. Lennox and Cobb<sup>3c</sup> expressed the belief that the occurrence of convulsions at menstruation is explained by the increased nervous irritability which many women exhibit at that time. Cases are reported of cessation of attacks following hysterectomy or castration. In one case in the series under discussion the patient had had three attacks—each one during pregnancy. Eclampsia<sup>55</sup> is an associated condition, although some authors consider that the eclampsia is due to hypertension rather than to a circulating toxin or an endocrine disturbance.

In summary, one may say that while an altered state of endocrine function is not infrequently found in epilepsy, it is uncommon to find such a condition bearing an etiologic relation to the seizures.

Disease of other organs occasionally produces epileptic seizures. In spite of reports to the contrary (Reed<sup>56</sup>), the gastro-intestinal tract is in rare instances the cause of an epileptic attack. Diseases of the respiratory system likewise play a little rôle in the production of convulsive seizures. "Pleural epilepsy" (Abadie<sup>57</sup>) has been described. After a

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52 Browning, W. The Question of Thymic Epilepsy, with Report of a Demonstrative Case, *M. Rec.* **98** 1013, 1920.

53 Wilder, J. Zur Neurologie und Psychiatrie der hypoglykämischen Zustände, *Med. Klin.* **26** 616, 1930.

54 Souques, A., and Gilbrin, E. Crises mensuelles d'épilepsie apparues après la suppression spontanée et précoce de la menstruation, *Rev. neurol.* **2** 109, 1930.  
Gordon, Alfred. Convulsive Disorders of Two Opposite Periods of Life. Puberty and Chmacterium, *Am. J. Psychiat.* **12** 929, 1933.

55 Campbell, W. E. The Eclamptic Convulsion, *Arch. Neurol. & Psychiat.* **20** 425 (Aug.) 1928.

56 Reed, Charles A. L. Some Typical Recoveries in Iowa from Chronic Convulsive Toxaemia (Epilepsy) Following Surgical Correction of the Abdominal Viscera, *J. Iowa M. Soc.* **10** 204, 1920.

57 Abadie, Jean. Modern Etiologic Conceptions of the Epilepsies, *Rev. neurol.* **1** 1041, 1932, abstr., *Arch. Neurol. & Psychiat.* **31** 1320 (June) 1934.

simple puncture of the pleura or pleural lavage, convulsive seizures have occurred. These are due to cerebral air or fluid embolism. In cases of mild involvement only syncopal attacks develop, but when the disease is severe status epilepticus may supervene. "Pleural epilepsy" is, however, rare. Hyperventilation may, by causing alkalosis, induce tetany or, more rarely, convulsions. In a small proportion of persons with epilepsy (25 per cent) an attack may be brought on by hyperventilation. Diseases of the circulatory system frequently initiate epileptic fits. Instances of convulsive attacks in Stokes-Adams' disease are numerous (Finny,<sup>58</sup> Russell<sup>59</sup> and Clark<sup>60</sup>). Attacks are seen occasionally in patients suffering from paroxysmal tachycardia (Clark<sup>60</sup>). They are of either the grand or the petit mal type. It is considered that they are due to cerebral anemia. In the present series there was a case of convulsive seizures associated with subacute endocarditis, the fits probably being due to cerebral emboli.

In uremic states with hypertension due to chronic nephritis, convulsions are common and may occur with few premonitory symptoms of the disease. The diagnosis may not be apparent if the patient is seen first at the time of the convulsion, but an analysis of the blood and the urine, together with the finding of hypertension, is usually sufficient to enable the physician to make the correct diagnosis. However, the presence of albumin in the urine does not necessarily indicate renal damage, as many persons with idiopathic epilepsy have albuminuria after an attack. Fishbeig and Oppenheimer<sup>25</sup> consider the fits in uremia as due to hypertension and claim that they are rare in cases of uncomplicated uremia. Foster,<sup>61</sup> however, isolated a toxic base from the blood of uremic patients which produces convulsive seizures in experimental animals.

#### THE PSYCHOGENIC FACTOR

Much has been written on the psychogenic factor in epilepsy. Some authors consider it the most important causative agent. Row and Bond<sup>62</sup> gave numerous reports of cases showing its influence. However, it is generally conceded that while psychogenic factors are undoubtedly present in every case they are rarely the most important elements. Clark<sup>63</sup>

58 Finny, J. M. Bradycardia, with Arrhythmia and Epileptiform Seizures, *Brit. M. J.* **1** 1967, 1906.

59 Russell, Alfred E. Some Disorders of the Cerebral Circulation and Their Clinical Manifestations, *Lancet* **1** 1963, 1909.

60 Clark, F. H. Occurrence of Epileptoid Attacks in Tachycardia and Bradycardia, *Brit. M. J.* **2** 308, 1907.

61 Foster, Nellis B. Uremia, *J. A. M. A.*, **76** 281 (Jan. 29) 1921.

62 Row, R. G., and Bond, W. E. Epilepsy: A Functional Mental Illness and Its Treatment, New York, Paul B. Hoeber, Inc., 1926, p. 138.

63 Clark, L. P. Psychology of Essential Epilepsy, *J. Nerv. & Ment. Dis.* **63** 575 1926.

and Rosett<sup>64</sup> both present interesting theories as to the psychogenic etiology of epilepsy

#### IDIOPATHIC EPILEPSY IN ADULT LIFE

Gowers<sup>65</sup> stated that in only 20 per cent of cases of idiopathic epilepsy does the condition begin in adult life. Study of the cases under consideration shows that less than half of all patients having epileptic attacks for the first time in adult life suffer from the idiopathic type. After the age of 50 that variety of epilepsy is practically unknown. In a person over 20 the diagnosis of idiopathic epilepsy is made only when every possible etiologic factor has been eliminated. Even then a careful watch is necessary for any further developments which might indicate that an organic cause has been overlooked.



Fig 1—Encephalograms of a patient in whom convulsive seizures developed after an injury to the head. Although both the physical and the neurologic examination gave essentially negative results, the encephalograms reveal a large cyst of the left frontal lobe.

Every adult presenting himself with the complaint of convulsive seizures should have a history taken with special reference to the disorders previously discussed and a complete physical and neurologic examination, as well as the routine laboratory tests, including a Wassermann and a Kahn test of the blood. If no abnormalities are revealed, roentgenograms of the skull should be taken. With such an examination the organic etiologic factors will be demonstrated in a majority of cases. A small percentage of patients, however, may harbor unrevealed gross intracranial pathologic conditions. For this reason it is advisable to

64 Rosett, J. The Mechanism and Fundamental Cause of the Epilepsies, *Arch Neurol & Psychiat* 9:689 (June) 1923.

65 Gowers, W. R. *Epilepsie and Other Chronic Convulsive Diseases*, London, J. & A. Churchill, 1881.

perform encephalography or ventriculography on every patient in whom there is no apparent cause for the seizures. Encephalographic findings frequently substantiate a provisional diagnosis or are sufficiently clear to make a definite diagnosis.

Thus, when clinical methods have been exhausted, encephalography enables the physician in a large percentage of cases to discover the organic etiologic factor when one exists. In posttraumatic epilepsy, encephalography usually reveals ventricular distortion or dilatation or some abnormality in the subarachnoid spaces. Foerster and Penfield<sup>66</sup> described the typical ventricular distortion as a wandering ventricle, the ventricle being drawn up at one point by scar tissue, with a subsequent shift of the entire ventricular system to that side. Occasionally a large cerebral cyst, such as the one illustrated in figure 1, is found.<sup>67</sup> Cere-



Fig 2—Encephalograms of a patient who had five generalized convulsions over a period of seventeen years. After the last attack, two years previous to his admission to the hospital, he had marked verbal aphasia and transient hemiparesis, of the right side. The encephalograms show an area of cortical atrophy in the distribution of the left prerolandic artery, probably due to scarring secondary to thrombosis of that vessel.

bral pathologic changes due to cerebral arteriosclerosis or degenerative disease of the central nervous system may be shown by encephalography when the changes are sufficient to produce an alteration in the shape or size of the cerebrum. The cerebral scarring secondary to a vascular accident is frequently well shown in an encephalogram (fig 2). Occa-

66 Foerster O, and Penfield, W. Der Narbenzug am und im Gehirn bei traumatischer Epilepsie in seiner Bedeutung für das Zustandekommen der Anfälle und für die therapeutische Bekämpfung derselben, *Ztschr f d ges Neurol u Psychiat* 125 475, 1930.

67 Dr Percival Bailey, of the University of Chicago Clinics, permitted the use of the encephalograms accompanying this article.

sionally, in the absence of any evidence of intracranial hypertension, a cerebral neoplasm is found by encephalography (fig 3). Intracranial pneumography allows a differentiation between two or more possible etiologic factors. Head injuries are so common now that there are few persons who have not suffered from cerebral concussion at some time, and yet to accept such an injury arbitrarily as an etiologic factor would lead to numerous errors. It is well known that many patients suffering from cerebral tumor date their symptoms from a head injury. The fact that a patient has a positive Wassermann reaction of the blood is no indication that he may not have an intracranial neoplasm, and if the course of his condition under therapy is not satisfactory, studies with air of his intracranial cerebrospinal fluid system may show the reason for the lack of response. Cerebral vascular disease is particularly difficult to distinguish from tumor in many cases. A slowly progressive loss of



Fig 3—Encephalographic findings in a case of parasagittal glioma producing epileptic attacks initiated by a tingling sensation of the right hand

cerebral function points to a neoplastic condition, but frequently it is necessary to resort to encephalography to make a definite diagnosis. Hypertension is not uncommonly associated with cerebral tumor, and hence one must not be content with a diagnosis of hypertension with symptomatic epilepsy, particularly if there are any atypical features.

If ventricular filling does not occur when encephalography is performed, it is essential to perform ventriculography, for one cause of nonfilling of the ventricles is the presence of an intracranial neoplasm. Even though considerable air is visualized in the subarachnoid spaces over the cerebral cortex (fig 4), a neoplasm may be present. Such findings have been encountered in several patients in whom subsequent ventriculography showed evidence of a cerebral tumor. For this reason any case of nonfilling of the cerebral ventricles during encephalography



should be considered a reason for suspecting tumor of the brain and a ventriculography should be performed

With the aid of tests with air one can make a definite diagnosis in some cases and in those instances in which the encephalogram reveals no abnormalities one may be fairly well satisfied that an etiologic factor which might be treated surgically has not been overlooked. Hence encephalography is a valuable adjunct to the diagnostic armamentarium of the neurologist or neurosurgeon in attacking the problem of the etiology of convulsive seizures originating in adult life. It enables him to diagnose or practically to eliminate tumor of the brain as an initiator of the attacks. By localizing the epileptogenous zone in cases of post-traumatic epilepsy it enables him to employ the method of cortical extirpation suggested by Foerster and Penfield<sup>66</sup> for the relief of



Fig 4—Anteroposterior and lateral encephalograms showing a large amount of air over the cerebral cortex, with an absence of ventricular filling, in a case of tumor of the left temporal lobe with symptomatic epilepsy

symptoms. In still other cases it presents evidence which may be the necessary confirmation of a clinical opinion.

#### SUMMARY

The conditions associated with convulsive seizures occurring for the first time in adult life in a series of one hundred cases are enumerated. While in by far the largest number of cases the etiologic factor was not known in many cases the patient was suffering from tumor of the brain, neurosyphilis or vascular hypertension with or without arteriosclerosis.

The conditions in which epilepsy may occur symptomatically are tabulated and discussed.

Encephalography is suggested as a valuable diagnostic adjunct which should be employed before a condition is pronounced idiopathic epilepsy.

# MORPHOLOGIC CHANGES IN THE HEART IN EXPERIMENTAL MYXEDEMA

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AND

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Cardiac enlargement and changes indicative of low voltage in the electrocardiogram have long been recognized as a part of the clinical picture of myxedema in the human being. The mechanism of the production of these signs is not well understood. With the introduction of the operation of total thyroidectomy as a therapeutic measure in chronic heart disease,<sup>1</sup> a knowledge of the exact nature of the changes which occur in the heart as a result of myxedema becomes of vital importance. With this in mind, experiments were planned which would enable us to study the effects of long-standing myxedema experimentally induced in animals. In the medical literature on the subject there is some confusion as to whether there are specific pathologic changes in the heart muscle in myxedema and still greater confusion as to whether these changes are responsible for the increase in the size of the heart and the changes of voltage in the electrocardiogram.

Ord<sup>2</sup> in 1880 described the heart of a patient with myxedema as being hypertrophied, flabby and dilated. Since then various cases have been reported, with a variety of pathologic changes. These include atheromatous changes in the large blood vessels, edematous swelling of the aortic leaflets, scars in the myocardium and edema of the heart muscle. Several authors, on the other hand, have denied the presence of any pathologic change in the heart in myxedema. These cases have recently been summarized by Ohler and Abramson.<sup>3</sup> Wegelin<sup>4</sup> in 1926

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From the Barbara Henry Research Laboratory of the Department of Medicine of the New York Hospital and Cornell University Medical College

1 Blumgart, H L, Riseman, J E F, Davis, D, and Berlin, D D. Therapeutic Effect of Total Ablation of the Normal Thyroid on Congestive Heart Failure and Angina Pectoris. III Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity, *Arch Int Med* **52** 165, 1933

2 Ord, W M. *Tr Clin Soc London* **13** 15, 1880

3 Ohler, W R, and Abramson, J. The Heart in Myxedema, *Arch Int Med* **53** 165, 1934

4 Wegelin, C, in Henke, F, and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol 8, p 353

said "The morphologic changes in the heart muscle in myxedema are not yet well understood" He further suggested that these apparent myocardial changes are due less to changes in the myocardium than to a decrease in the number of red blood cells and to bradycardia

Several attempts have been made to study the pathologic changes resulting from myxedema experimentally induced in animals Cretinism and myxedema have been confused in some of these studies, with the result that conclusions in regard to myxedema have been drawn on the findings produced by thyroidectomizing very young animals There is wide disagreement in these experimental results

Tatum<sup>5</sup> studied the histologic changes produced by thyroidectomy in rabbits weighing from 150 to 250 Gm He reported degeneration of the myocardium, with swelling of the individual muscle cells Benson<sup>6</sup> thyroidectomized adult rabbits and detected slight granular degeneration of the heart muscle He considered these changes relatively slight Kishi<sup>7</sup> thyroidectomized cats and dogs and noted little change in the histologic appearance of the heart muscle Brooks and Larkin<sup>8</sup> reported no alteration in the myocardium of thyroidectomized adult rabbits However, their animals were kept for a relatively short period Goldbeig<sup>9</sup> in 1927 studied the changes produced by thyroidectomy in the cardiovascular systems of young sheep He noted calcification of the aorta and cardiac dilatation in these myxedematous animals but apparently was not impressed by any cytologic change in the heart muscle

#### METHODS

The following experiment was planned in an effort to determine whether definite morphologic changes can be produced in the heart muscle of adult rabbits as a result of myxedema and if possible to ascertain the significance of these changes

Four litters consisting of sixteen young adult Belgian rabbits weighing between 1,800 and 2,400 Gm were divided into two groups Five animals were set aside as controls Three died during operative procedures The remaining eight were successfully subjected to total thyroidectomy The operation was performed with the animal under ether anesthesia The thyroid isthmus was dissected free from the trachea and divided The lobes were then removed separately, care being taken to avoid the recurrent laryngeal nerves and to free completely the superior poles of the gland These animals made an uneventful postoperative recovery

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5 Tatum, A L J Exper Med **17** 636, 1913

6 Benson, W Virchows Arch f path Anat **170** 229, 1902

7 Kishi, K Virchows Arch f path Anat **176** 260, 1904

8 Brooks, H, and Larkin, J Am J M Sc **155** 66, 1918

9 Goldbeig, S A Quart J Exper Physiol **17** 15, 1927

All the animals were maintained in individual cages and were fed a standard diet of alfalfa hay, oats and water, with green vegetables twice a week. The body weights were determined weekly. The rabbits of both the control and the thyroidectomized series remained in good health throughout the experiment.

Within three weeks after operation, the thyroidectomized animals began to show clinical evidence of myxedema. The fur became thin, and later actual bare areas developed. The movements were sluggish. No peripheral edema was noted. After some weeks there appeared to be an increase in the size of the abdomen. The myxedematous animals tended to gain weight more rapidly than those of the control series. The blood cholesterol level was used as an index of the severity of the myxedema. Approximately three months after operation three of the animals appeared to be recovering from the myxedema. Their blood cholesterol levels became normal. With the animal under ether anesthesia, the thyroid region was explored. Small areas of regenerated thyroid tissue were found in the region of the isthmus. These were removed by dissection and cautery, and the animals were returned to the experimental group. They again began to show clinical signs of myxedema at the end of from two to three weeks.

Electrocardiographic tracings were taken at intervals throughout the experiment for both the control and the experimental animals. The changes in voltage of the QRS complex and the height of the T wave were used as an adjunct to the clinical findings, and the blood cholesterol level was used as an index of the degree of myxedema and the state of the cardiac musculature. The three standard leads were employed. Contact was made by moistening the closely clipped legs with a solution of sodium chloride and wrapping them in wet flannel bandages, around which were several turns of copper wire to which the leads were attached.

The experiment was terminated from five to seven months after thyroidectomy. The animals were killed by carbon monoxide gas in a respiration chamber. Autopsy was performed immediately. The heart was removed, the great vessels were cut at a constant length, and all the blood contained in the chambers was allowed to drain out. The weight of the heart was taken. A segment of ventricle approximately 2 cm square was then removed and weighed. This was dried for three days at 40 C and again weighed. The loss of weight was used as a basis for the calculation of the fluid content of the heart. Tissue was taken from all organs of the body for microscopic examination. Segments were removed from both the left ventricle and the auricle of the heart in all animals. These were stained with hematoxylin and eosin and with sudan IV.

## RESULTS

The control series of animals showed no abnormal changes at autopsy. The cardiac weights are shown in table 1. Microscopic examination showed normal heart muscle (figs 1 and 2). All other organs were normal.

The changes in the myxedematous animals, on the other hand, were striking. There was some variation in the degree of myxedema present. Three animals (106, 107 and 108) were extremely myxedematous. Their blood cholesterol levels ranged between 305 and 330 mg per hundred cubic centimeters. In the remaining five the condition was moderately severe but did not reach the stage of causing

effusions into the serous cavities of the body. They all showed a marked decrease in the amount of hair. Actual bald areas existed on several of the animals. There was no peripheral edema. The region of the neck was searched for evidence of thyroid tissue. In two of the rabbits (100 and 111) a cluster of cells approximately 1 mm square was found over the trachea. Three animals (106, 107 and 108) showed several cubic centimeters of fluid in the pericardial cavity. These same animals each had approximately 150 cc of fluid in the abdominal cavity. The

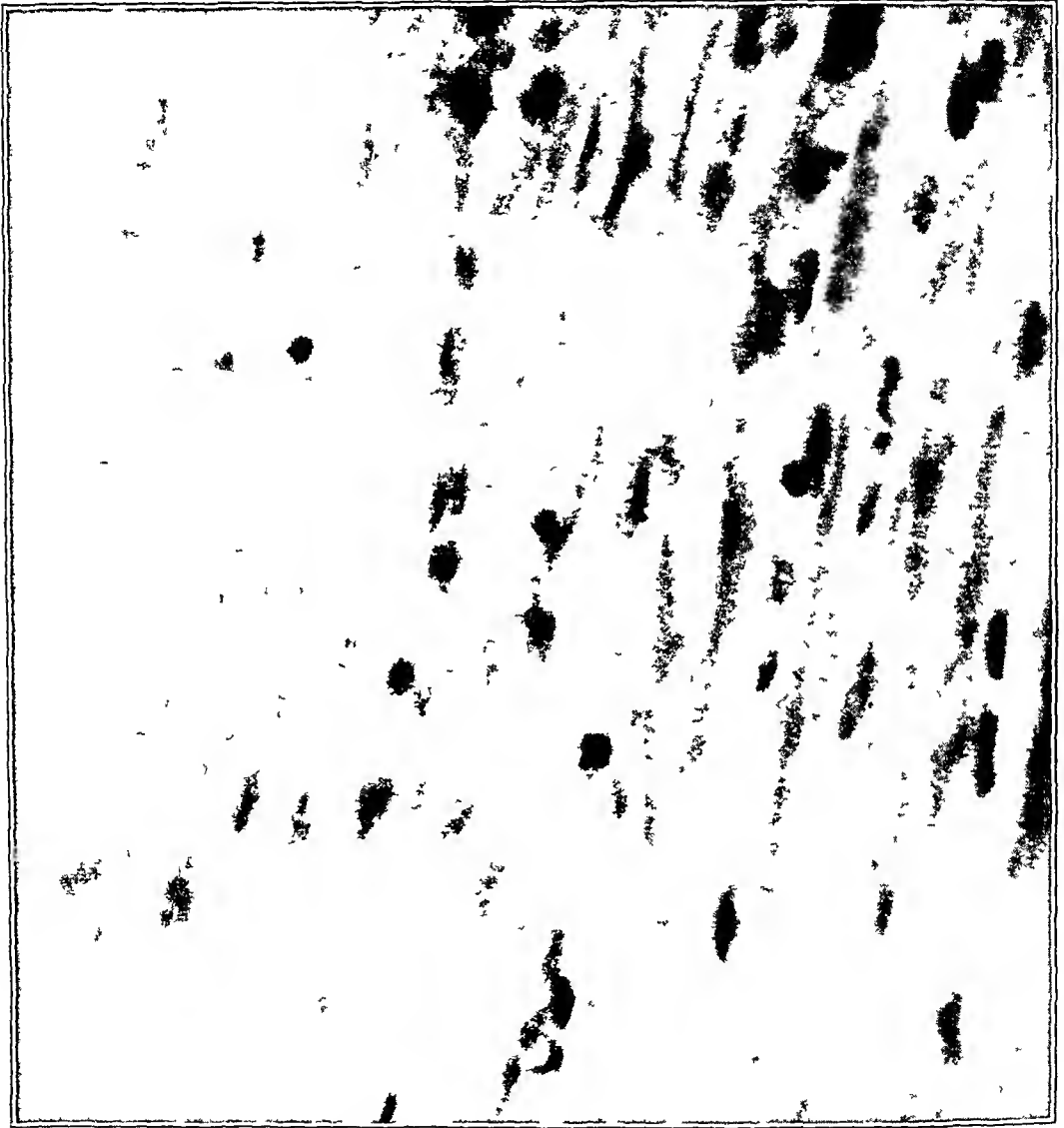


Fig 1—Photomicrograph of the heart muscle of rabbit 101, a normal control ( $\times 700$ )

hearts of all the myxedematous animals were pale and flabby, in comparison with those of the normal controls. No changes were observed in the aorta. There were some fatty degeneration of the liver and marked atrophy of the germinal epithelium of the testes and the follicular portion of the ovaries.

The fluid content of the heart muscle, as determined by desiccation of a segment, is shown in table 1. The average percentage of fluid in the myxedematous

hearts was 819, while in the control series it was 756. The fluid content was highest in the three animals which showed the greatest clinical evidence of myxedema.

*Microscopic Examination*—The heart muscle of the myxedematous animals took the hematoxylin and eosin stain less well than did that of the normal control animals. There was a striking increase in the size of the spaces between the individual fibers. The fibers themselves were swollen, and there was a decrease

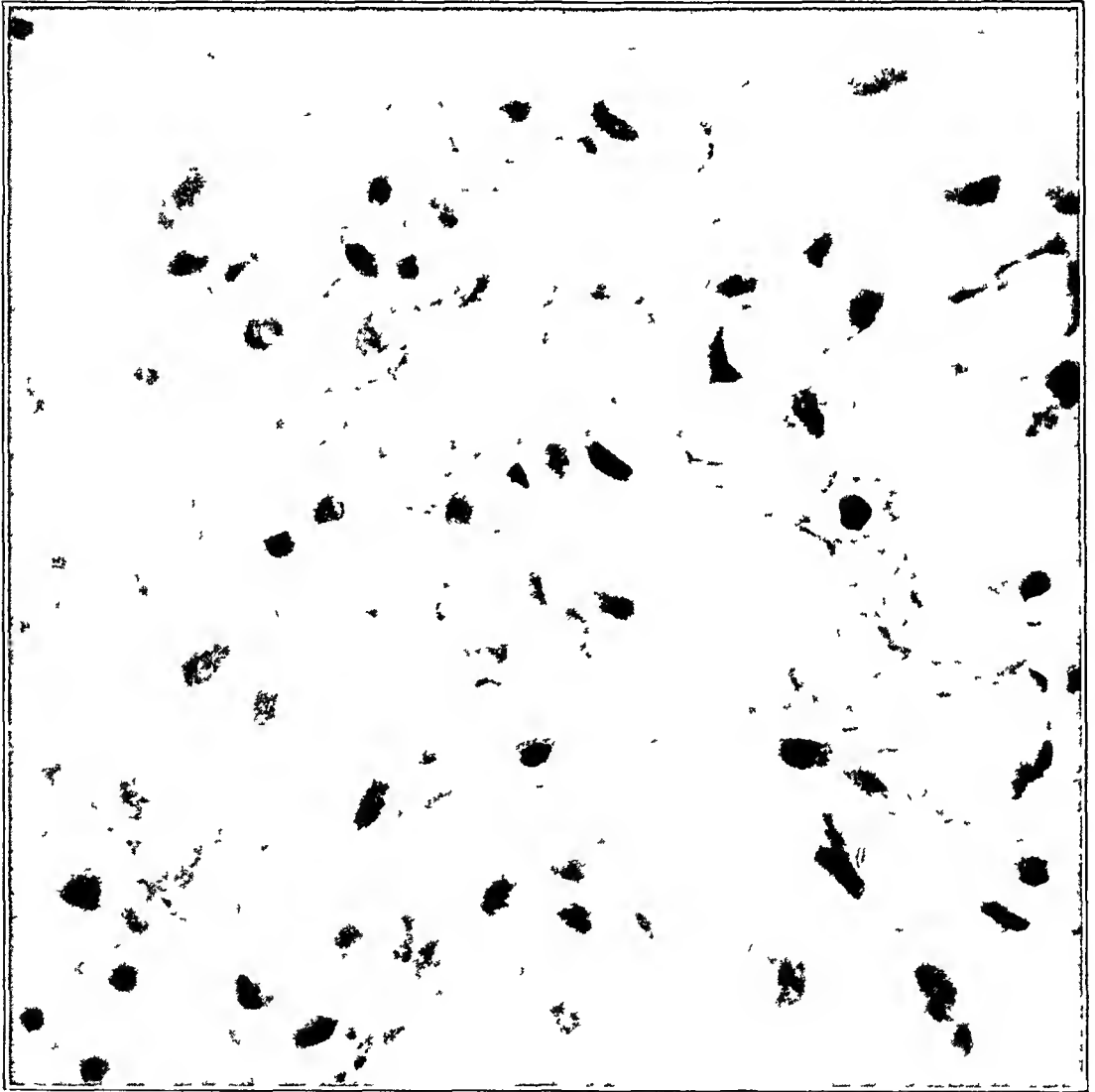


Fig 2—Photomicrograph of the heart muscle of rabbit 101, a normal control, showing fibers in cross-section ( $\times 700$ )

in the actual number of fibers per square millimeter. There was an increase in prominence of the longitudinal striation and partial disappearance of the transverse striation. The nuclei were surrounded by a clear space and were pyknotic, tending to stain deeply. This increase in the perinuclear space is shown clearly in a cross-section of the muscle bundle (fig 3). Frozen sections stained with sudan IV showed that there was little fat in the heart muscle. The clear spaces around the nuclei and between the fibers did not contain fat.

No definite changes could be made out in the aortas of the myxedematous animals. There was a definite atrophy of the germinal epithelium of the testes in the males and of the follicular portion of the ovaries in the females. There was some increase in the eosinophilic element of the pituitary. No other constant changes were observed in the myxedematous animals.

*Electrocardiographic Findings*—The electrocardiographic tracings were intended primarily as an index of the degree of myxedema. In general, the voltage, as indi-



Fig 3—Photomicrograph of the heart muscle of rabbit 106, showing changes produced by myxedema ( $\times 700$ )

cated by the changes in the height of the T wave and of the QRS complex, decreased with the development of the myxedema. These findings, however, were not as constant as would be expected from the present knowledge of myxedema in human patients. This may have been due to faulty or inconstant contacts of the various leads.

*Protocol*—The protocol of one animal is given in detail. The observations on the others are summarized in table 2.

**RABBIT 106**—An adult female Belgian rabbit was admitted to the laboratory on July 1, 1934. The weight was 1,750 Gm. Total thyroidectomy with the animal under ether anesthesia was performed on July 10, 1934. On Aug. 23, 1934, it was

TABLE 1—*Weight and Fluid Content of the Hearts of Control and Thyroidectomized Rabbits*

Rabbit No	Body Weight, Gm	Weight of Heart, Gm	Heart Weight Body Weight Ratio	Percentage of Fluid in Heart Muscle
Control Series				
101	3,425	7.36	465.3	77.6
102	3,144	7.28	433.2	74.3
103	3,355	7.31	458.9	76.2
104	2,700	7.10	340.3	75.8
110	3,425	7.19	476.4	74.2
Thyroidectomized Series				
100	2,830	6.87	412.0	81.7
105	2,900	6.29	461.0	79.6
106	2,691	5.65	476.3	83.8
107	3,159	5.74	550.4	84.4
108	2,857	5.71	500.4	84.8
109	2,380	4.67	509.6	79.8
111	2,800	6.40	437.9	80.1
112	2,500	4.62	541.1	81.0

TABLE 2—*Summary of Changes Observed at Autopsy*

Rabbit No	Number of Days Since Operation	Clinical State	Gross Observations (Other Than Heart)	Microscopic Observations (Extent of Myocardial Changes)
100	142	Moderate myxedema	Minute area of thyroid tissue over trachea	Moderate degeneration
105	188	Moderate myxedema		Moderate degeneration
106	185	Extreme myxedema	Fluid in pericardial sac and peritoneum	Marked degeneration
107	175	Extreme myxedema	Fluid in pericardial sac and peritoneum	Marked degeneration
108	178	Extreme myxedema	Fluid in pericardial sac and peritoneum	Marked degeneration
109	180	Moderate myxedema		Moderate degeneration
111	119	Moderate myxedema	Minute area of thyroid tissue over trachea	Moderate degeneration
112	153	Moderate myxedema		Moderate degeneration

noted that the animal had several bald spots and that its coat was dull and unhealthy looking. On Nov. 1, 1934, it had a definite mangy appearance. The cholesterol content of the blood at that time was 305 mg per hundred cubic centimeters. The animal was killed on Jan. 12, 1935, one hundred and eighty-five days after operation. The body weight at that time was 2,691 Gm.



At autopsy the hair was scanty and lacked luster. The abdomen was distended. No thyroid tissue was found. The thymus gland was atrophic. There was no pleural effusion.

The pericardium was distended with clear fluid. The heart was flabby and soft. It weighed 5.65 Gm. and contained 83.8 per cent of fluid.

The abdomen contained several hundred cubic centimeters of clear fluid. The adrenal glands were within the normal weight range. All other organs were grossly normal.

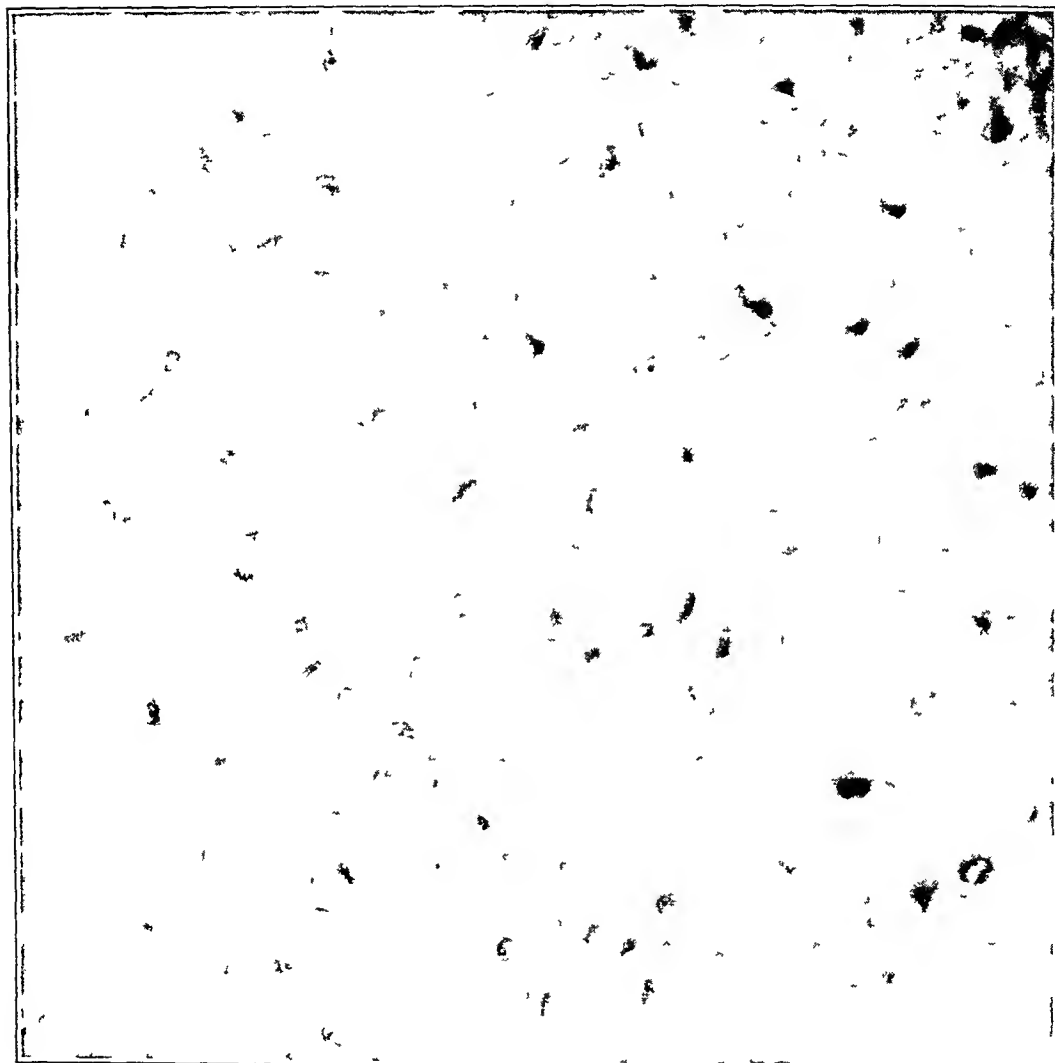


Fig. 4—Photomicrograph of the heart muscle of rabbit 106, showing changes produced by myxedema in cross-section of fibers ( $\times 700$ )

#### SUMMARY

Myxedema was readily produced in adult rabbits by total removal of the thyroid gland. In the cases of more severe involvement this was accompanied by pericardial and peritoneal effusions. The heart muscle of these myxedematous animals had an average fluid content of 81.9

per cent, as compared with 75.6 per cent in a control series of normal animals. On microscopic examination this heart muscle showed marked degenerative changes, characterized by a decrease in the number of fibers, edema and a disappearance of the perinuclear sarcoplasm.

Myxedema is apparently capable of producing serious myocardial damage in the adult rabbit.

# EFFECT OF ALKALINE THERAPY FOR PEPTIC ULCER ON UTILIZATION OF DIETARY IRON IN THE REGENERATION OF HEMOGLOBIN

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AND

STACY R METTIER, M D

SAN FRANCISCO

Loss of blood over a long period leads to hypochromic anemia, which may properly be attributed to depletion of the iron stored in the body. Regeneration of hemoglobin in patients with uncomplicated anemia of this type occurs after cessation of the hemorrhage with the aid of appropriate iron therapy. One of the frequent causes of this type of anemia is prolonged or recurrent loss of blood from a peptic ulcer. In patients with depletion of stored iron due to a bleeding ulcer, dietary iron alone is insufficient to stimulate rapid formation of hemoglobin, and chronic anemia often persists after the bleeding is stopped.

A common method of treating peptic ulcer is the modified Sippy regimen. This requires the use of large amounts of alkaline powders daily over a long period. Such treatment obviously renders alkaline the contents of the upper part of the gastro-intestinal tract. In recent years it has been shown that an alkaline  $p_H$  of the gastro-intestinal tract is unfavorable for the absorption of metallic substances, such as calcium and phosphorus, and Mettier and Minot<sup>1</sup> have shown that small doses of iron are better utilized from an acid duodenal content than from a neutral or alkaline one. In addition, Reimann and Fritsch<sup>2</sup> and Bethell, Goldhamer, Isaacs and Sturgis<sup>3</sup> have reported that iron is more rapidly effective in patients with normal gastric secretion than in those with achlorhydria.

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This study was aided by the Christine Breon Fund for Medical Research

1 Mettier, S R, and Minot, G R. The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastro-Duodenal Contents in Certain Cases of Anemia, *Am J M Sc* **181** 25 (Jan) 1931

2 Reimann, F, and Fritsch, F. Experimentelle und klinische Untersuchungen über die Wirkung des Ferrum reductum, *Ztschr f klin Med* **117** 304, 1931

3 Bethell, F H, Goldhamer, S M, Isaacs, R, and Sturgis, C C. Diagnosis and Treatment of Iron-Deficiency Anemias, *J A M A* **103** 797 (Sept 15) 1934

Ordinarily, patients with peptic ulcer secrete a gastric juice high in acid content. It occurred to us, however, that alkalization might influence unfavorably the utilization of dietary iron and thus account for prolonged periods of anemia. It seemed desirable, therefore, to study the production of hemoglobin during the ingestion of dietary iron in patients undergoing alkaline therapy for peptic ulcer. Accordingly, four patients were selected for observation whose reserves of iron had been depleted by recurrent loss of blood from the bowel.

#### TYPE OF PATIENTS AND METHOD OF STUDY

All four patients were men. They varied in age from 37 to 61 years. Each one gave a history of prolonged loss of blood from the gastro-intestinal tract. In one patient bleeding had been noticed for six months, and in the others, for one or more years. Prior to the starting of our investigation bleeding had stopped. The diagnoses of peptic ulcer were substantiated by roentgen ray examination.

The anemia was of the hypochromic type, and in none of the patients was there clinical evidence of infection or a malignant process that might account for it.

Fractional analyses showed the presence of free hydrochloric acid in the contents of the stomachs of all four patients during fasting.

Daily examinations of the blood were made, including estimations of the hemoglobin content and erythrocyte and reticulocyte counts. The concentration of hemoglobin was determined with a Sahli hemometer calibrated so that 100 per cent equaled 14 Gm. of hemoglobin per hundred cubic centimeters of blood. The stools were examined frequently for macroscopic and occult blood to determine whether or not hemorrhage recurred.

The clinical data for the patients studied are shown in the table.

#### *Clinical Data*

No	Patient	Sex	Age	History	Gastric Secretion
1	R B	M	53	Duodenal ulcer with bleeding for one year, tarry stools for two months	Fasting, 4 cc N/10 HCl per 100 cc, after histamine, 11 cc N/10 HCl per 100 cc
2	W D	M	37	Duodenal ulcer with tarry stools for one year	Fasting, 5 cc N/10 HCl per 100 cc, after histamine, 55 cc N/10 HCl per 100 cc
3	J McK	M	61	Recurrent gastric ulcer, gastro-enterostomy one year previously, tarry stools for six months, generalized arteriosclerosis	Fasting, free HCl present
4	J M M	M	60	Recurrent duodenal ulcer, hematemesis three years previously, gastro-enterostomy one year previously, tarry stools for one month	Fasting, 15 cc N/10 HCl per 100 cc, after histamine, 77 cc N/10 HCl per 100 cc

The method of alkalizing the upper part of the gastro-intestinal tract was based on a modified Sippy regimen. It consisted of the administration of an alkaline powder every two hours throughout the day and of 200 cc of whole milk or milk and cream at alternate hours. This diet is decidedly poor in iron. The total daily consumption of alkalis amounted to from 11 to 19 Gm. of sodium bicarbonate, from 3 to 5 Gm. of calcium carbonate and from 1 to 2 Gm. of magnesium oxide.

## OBSERVATIONS

During the period of alkaline therapy and restriction of the intake of iron there was no significant increase in hemoglobin concentration (charts 1, 2, 3 and 4) The number of erythrocytes failed to increase

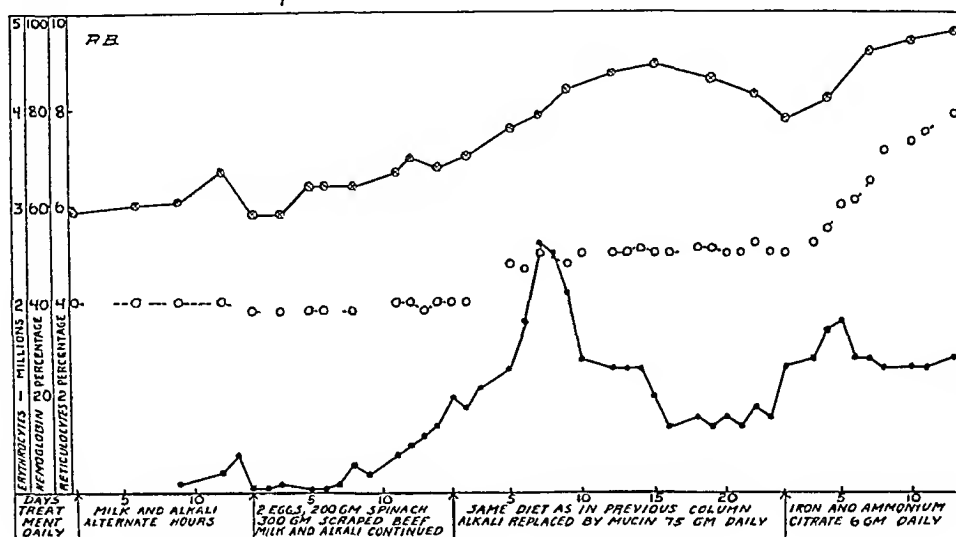


Chart 1—Curves showing the ineffectiveness of an iron-rich diet on the formation of hemoglobin in patient 1 while he was undergoing alkaline therapy, the moderate response after the withdrawal of alkalis and the increase in red blood cells after the addition of dietary iron In the charts the curve of circles with X and a straight line indicates red blood cells in millions per cubic millimeter, the curve of circles and dashes, the percentage of hemoglobin content, and the curve of dots and a straight line, the percentage of reticulocytes

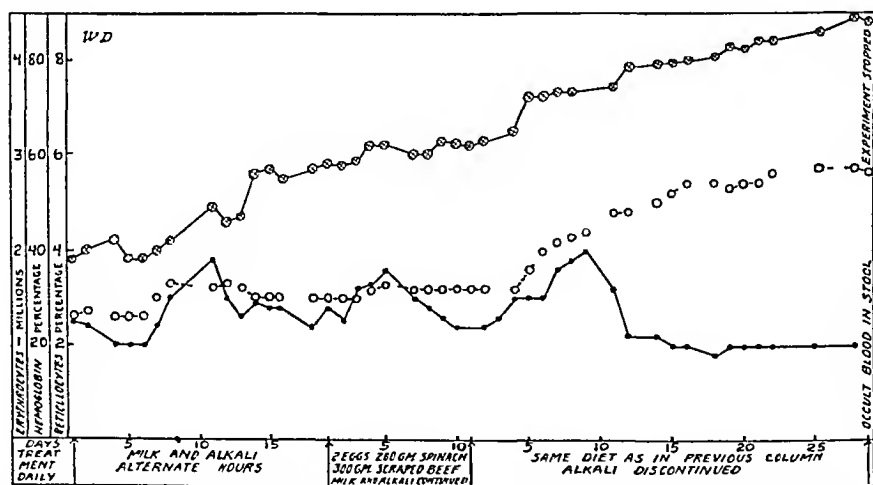


Chart 2—Curves showing the ineffectiveness of an iron-rich diet on the formation of hemoglobin in patient 2 while he was undergoing alkaline therapy and the satisfactory response after the withdrawal of alkalis

significantly except in one patient (chart 2), in whom there was a rise in the number of red blood cells from 2,000,000 to 2,800,000 per cubic

millimeter This reaction on the part of the bone marrow may be interpreted to indicate a decided depletion in the reserves of the substances necessary for the synthesis of hemoglobin and also, except in one patient, a lack of stroma-building material available for the production of erythrocytes

#### EFFECT OF DIETARY IRON DURING ALKALINIZATION

In the second period of study the administration of alkaline powders was continued, but the diet was supplemented by foods containing iron. Sherman<sup>4</sup> stated that the daily requirement of iron is from 12 to 15 mg. Mettier, Kellogg and Rinehart<sup>5</sup> have shown that the daily administration of a meal predigested with pepsin and hydrochloric acid and containing that amount of iron causes a rapid and satisfactory increase in concentration of hemoglobin in patients with idiopathic hypochromic

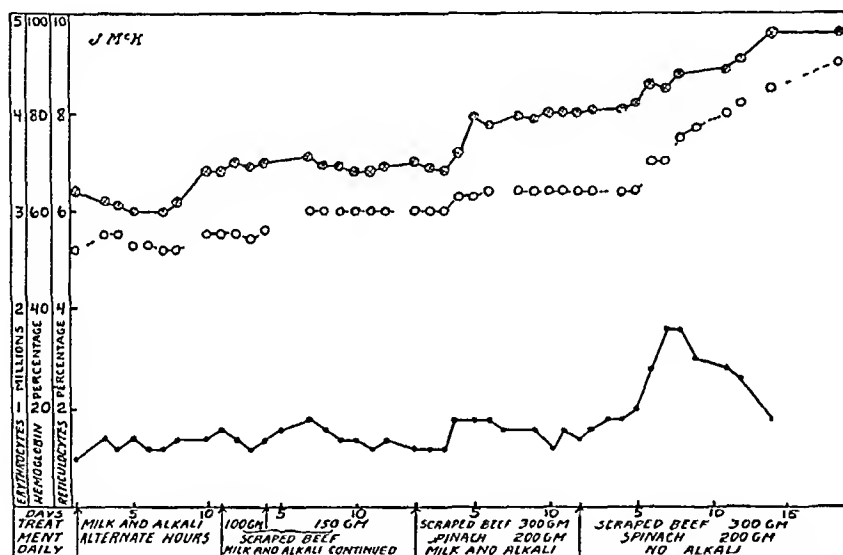


Chart 3—Curves showing the relative ineffectiveness of an iron-rich diet on the formation of blood in patient 3 while he was on an alkaline regimen and the satisfactory response after the withdrawal of alkalis

anemia Accordingly, cooked eggs, spinach and scraped beef, containing from 12 to 15 mg of iron, were given daily Vitamin C was provided by the ingestion of small amounts of orange juice

The addition of this diet to the alkaline regimen was not followed by an appreciable increase in production of hemoglobin In one patient

4 Sherman, H C Chemistry of Food and Nutrition, ed 3, New York, The Macmillan Company, 1926, p 340

5 Mettier, S R, Kellogg, F, and Rinehart, J F Chronic Idiopathic Hypochromic Anemia Etiologic Relationship of Achlorhydria to the Anemia, with Special Reference to the Effect of Large Doses of Iron, Organic (Dietary) Iron and of Predigested Food upon Formation of Erythrocytes, Am J M Sc 186 694 (Nov) 1933

(chart 3) there was a rise in the concentration of hemoglobin from 55 to 60 per cent, and after the diet had been increased twofold, a rise from 60 to 64 per cent (These slight increases are in decided contrast to the subsequent changes in the concentration of hemoglobin in the same patient )

Definite increases in the number of erythrocytes occurred in all patients, although three (charts 1, 3 and 4) had previously shown no increase. This suggested that material necessary for the formation of stroma or for the maturation of erythrocytes was now being absorbed from the foods which had been added to the diet.

In order to determine whether or not alkalinization had unfavorably influenced the utilization of iron derived from food, the use of the powders was stopped, but the diet rich in iron was continued.

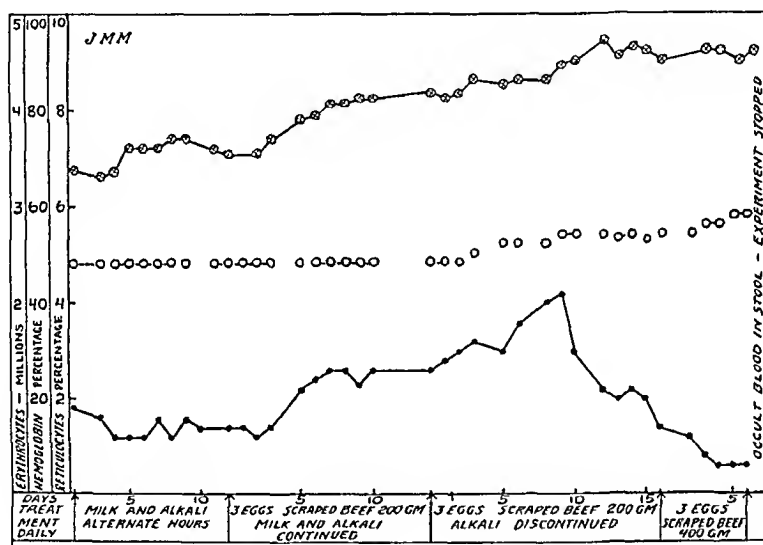


Chart 4—Curves showing the ineffectiveness of an iron-rich diet on the formation of hemoglobin in patient 4 during alkaline therapy and the slight response after the withdrawal of alkalis

#### EFFECT OF DIETARY IRON WITHOUT ALKALINIZATION

Beginning on about the fourth to the sixth day after this change in therapy there was a rise in hemoglobin concentration in all four patients. For a period of from twenty to thirty days previously it had been 40, 32, 64 and 48 per cent, respectively, whereas twenty days after the change it had increased to 51, 56, 90 and 58 per cent. The increase in two patients (charts 2 and 3) was in excess of 1 per cent a day, which represents a satisfactory rate and one comparable to that produced by adequate iron therapy<sup>6</sup>. In one patient (chart 4) the experiment was

<sup>6</sup> Heath, C W. Oral Administration of Iron in Hypochromic Anemia, Arch Int Med 51 459 (March) 1933

stopped because of the recurrence of bleeding. In the fourth (chart 1) the substitution of 90 Gm of mucin for the alkaline powders, with consequent partial neutralization of gastric acidity, may have modified the utilization of the dietary iron. The subsequent ingestion of iron and ammonium citrates (U S P, 6 Gm daily) by the third and fourth patients induced a rapid rise in the hemoglobin content.

Coincident with the increase in hemoglobin there was a rise in the percentage of reticulocytes, which was marked in two patients (charts 1 and 3), and a further increase in the number of erythrocytes. Thus the response of the bone marrow to the withdrawal of alkaline therapy resembled qualitatively in each patient and quantitatively in two patients the response which is produced by the ingestion of large doses of inorganic iron. This fact becomes more striking when one considers the relatively small amounts of iron present in the diet administered.

#### COMMENT

The data obtained from the examination of the blood of four men with anemia secondary to prolonged loss of blood from a peptic ulcer serve to illustrate the changes which may take place in the formation of blood as a result of the administration of an iron-rich diet, first, while the upper part of the gastro-intestinal tract is made alkaline by a modified Sippy regimen and, second, after the alkaline therapy is discontinued. It was demonstrated that an iron-rich diet had practically no effect on the formation of hemoglobin during the period of alkalimization but that after the administration of alkalis was stopped it had a marked effect, comparable to that produced by adequate therapy with inorganic iron.

Apparently, therefore, alkaline therapy interferes with the utilization of dietary iron. Alkalimization of the upper part of the gastro-intestinal tract depresses peptic digestion and alters the  $p_H$  of this section of the intestinal tract. Both effects interfere with the digestion and the assimilation of iron in the food and explain the lack of formation of hemoglobin during the period of alkaline therapy.

This state of impaired utilization of iron for the formation of blood resembles closely that existing in patients with idiopathic hypochromic anemia. Such patients have been shown<sup>5</sup> to be suffering from an iron deficiency anemia wherein gastric dysfunction leads to failure in utilization of dietary iron. Thus the altered formation of hemoglobin seems to depend on the same mechanism in patients with chronic idiopathic hypochromic anemia and in the patients here discussed, in whom digestion and the  $p_H$  of the upper part of the gastro-intestinal tract were artificially altered by alkaline therapy.



Hence the present observations reemphasize the importance of the rôle of normal gastric acidity in the utilization of dietary iron for the formation of hemoglobin. In patients under alkaline treatment for peptic ulcer complicated by iron deficiency anemia, the anemia will not become less until alkalization is discontinued, so as to allow utilization of dietary iron, or until large doses of inorganic iron are administered. From a practical standpoint, the latter treatment is the method of choice, as the foods containing large amounts of iron are those which favor a recurrence of peptic ulcer, especially in the absence of alkaline therapy.

#### SUMMARY AND CONCLUSIONS

Data are presented on the influence of alkalization of the gastrointestinal tract, as carried out with a modified Sippy regimen, on the regeneration of blood by dietary iron in a group of four men with anemia following prolonged bleeding from a peptic ulcer.

The response of the bone marrow, as determined by the production of hemoglobin and erythrocytes, to dietary iron with alkaline therapy is compared to the response of the bone marrow to the same amounts of dietary iron after cessation of the alkaline regimen.

The bone marrow failed to respond to the ingestion of dietary iron while the patients were undergoing the alkaline therapy, but on withdrawal of the alkaline regimen an increase in concentration of hemoglobin occurred. In contrast, increases in the number of erythrocytes and reticulocytes occurred soon after the addition of the iron-rich diet to the alkaline regimen.

It is concluded that alkalization of the upper part of the gastrointestinal tract interferes with the utilization of dietary iron for the synthesis of hemoglobin but not with the utilization of material necessary for the formation of erythrocyte stroma.

Mrs Katherine Purviance made the blood counts for our patients.

# ETIOLOGIC SIGNIFICANCE OF STREPTOCOCCI IN EPIDEMIC ENCEPHALITIS

I INCIDENCE OF STREPTOCOCCI IN CULTURES FROM PATIENTS WITH  
ENCEPHALITIS IN ST LOUIS AND FROM NORMAL CONTROLS, AND  
CHARACTERISTICS OF THE VARIOUS STRAINS ISOLATED

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The outbreak of acute epidemic encephalitis in St Louis in the summer of 1933 offered an especially propitious opportunity to investigate the etiologic importance of streptococci in this disease as a parallel study to that being carried on with the filtrable virus by our associates. We were further stimulated to undertake this work by the presence in St Louis of Dr E C Rosenow, who was studying this same question and who was accumulating evidence similar to that advanced by him in the past indicating, in his opinion, the primary rôle of streptococci in the causation of the St Louis form of the disease.

In view of the prominence of Rosenow's work in this field and in consideration of the fact that his results have been attained by following a special technic, our efforts were confined largely to a repetition of his studies, with as nearly as possible identical methods. We made a particular effort to learn the details of his technic and to follow it precisely. In this we had the full cooperation of Dr Rosenow, who visited our laboratory repeatedly and gave us a complete demonstration of his procedures.

The results of this investigation are reported in two papers. In the present communication the incidence of streptococci in cultures from

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This investigation was undertaken as a part of the general study of the etiology of encephalitis conducted under the auspices of the Metropolitan Health Council of St Louis during the epidemic of acute encephalitis in the summer of 1933. A summary appears in Public Health Bulletin 214 of the United States Public Health Service.

From the department of bacteriology and immunology, Washington University School of Medicine

patients with encephalitis and from normal controls and the cataphoretic velocity, agglutination reactions and general characteristics of the organisms in these cultures are discussed. In the second paper experiments with animals, designed to investigate the question of the etiologic relationship to clinical encephalitis of the several strains of streptococci studied, are described, and the conclusions drawn from the whole study are given.

#### REVIEW OF THE LITERATURE CONCERNING THE ETIOLOGIC RELATIONSHIP OF STREPTOCOCCI TO ENCEPHALITIS

Since the recognition of epidemic encephalitis as a distinct clinical entity by von Economo in 1917, numerous investigators have sought to discover the specific etiologic agent among the bacteria or among the filtrable viruses. Observations suggesting a bacterial causation of this disease were reported early, and a few workers, notably Rosenow, have consistently upheld the view that certain visible and cultivable microorganisms are of primary etiologic importance. On the other hand, the failure to cultivate any bacteria from human tissues in many cases and the obvious analogy with known virus diseases in respect to clinical, pathologic and epidemiologic features have led the majority of investigators to believe that the etiologic agent of epidemic encephalitis must be an ultramicroscopic virus. Unfortunately, attempts on the part of several groups of workers to isolate and identify a specific virus through inoculation of animals gave divergent and inconclusive results, particularly in the many researches in which rabbits were used as the experimental animals. This was due in part to the occurrence of spontaneous encephalitis in rabbits and in part to confusion of the hypothetical virus of encephalitis with the virus of herpes or of rabies, or with other viruses producing symptoms in rabbits.

However, well documented evidence in favor of a specific filtrable virus, distinct from the virus of herpes, as the etiologic agent of encephalitis was brought forward by McIntosh<sup>1</sup> in the Derby epidemic in England in 1919 as well as by Takagi,<sup>2</sup> who investigated the epidemic of

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1 McIntosh, J. Transmission of Experimental Encephalitis Lethargica in a Series of Monkeys and Rabbits, with Notes on Spontaneous Infection in the Monkey, *Brit J Exper Path* **1** 257 (Oct.) 1920. McIntosh, J. A., and Turnbull, H. M. Experimental Transmission of Encephalitis Lethargica to the Monkey, *ibid* **1** 89 (April) 1920.

2 Takagi, I. Etiology of Encephalitis Occurring Epidemically in Japan in 1924, *Japan M World* **5** 147 (June) 1925, *Virus of Encephalitis Japonica*, *Ztschr f Immunitätsforsch u exper Therap* **47** 441, 1926.

1924 in Japan. Nevertheless, the conclusion reached by several authors<sup>3</sup> of recent authoritative reviews of this subject seemed to be that the true nature of the etiologic agent had not as yet been clearly established, although a filtrable virus was the most likely cause of epidemic encephalitis.

The study of the acute form of encephalitis in the St. Louis epidemic of 1933 brought definite evidence for the virus etiology. Muckenfuss, Armstrong and McCordock<sup>4</sup> as well as Webster and Fite<sup>5</sup> recovered from the brains of patients with fatal encephalitis a filtrable virus which reproduced in monkeys and in mice clinical symptoms and pathologic changes closely resembling in most of their features the picture of encephalitis in human beings. Further, they showed that this virus is specifically neutralized by the serum of convalescent or recovered patients<sup>6</sup>. The pathologic changes produced by the virus in mice have been described more fully by Smadel and Moore<sup>7</sup>. The results of these investigations seem to leave little doubt as to the primary etiologic rôle played by a specific filtrable virus in the form of epidemic encephalitis which occurred in St. Louis, and they lend weight to the view that other outbreaks of this disease may have been due to a similar, if not identical, virus.

On the other hand, the possible etiologic importance of streptococci has been repeatedly suggested since the earliest description of epidemic encephalitis as a specific disease. Von Weisner,<sup>8</sup> in 1917, inoculated a

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3 (a) Zimsser, H. Present State of Knowledge Regarding Epidemic Encephalitis. Thirteenth Mellon Lecture, Arch Path **6** 271 (Aug.) 1928. (b) Neal, J. B. Present Status of the Etiology of Epidemic Encephalitis, J. A. M. A **91** 231 (July 28) 1928. (c) Stern, F. Die epidemische Encephalitis, ed 2, Berlin, Julius Springer, 1928. (d) von Economo, C. Die Encephalitis lethargica, ihre Nachkrankheiten und ihre Behandlung, Berlin, Urban & Schwarzenberg, 1929. (e) Levaditi, C. Etiology of Epidemic Encephalitis. Its Relation to Herpes, Epidemic Poliomyelitis and Post-Vaccinal Encephalopathy, Arch Neurol & Psychiat **22** 767 (Oct.) 1929. (f) Epidemic Encephalitis. Etiology, Epidemiology, Treatment, Report of a Survey by the Mathewson Commission, New York, Columbia University Press, 1929. (g) Second Report, 1932.

4 Muckenfuss, R. S., Armstrong, C., and McCordock, H. A. Encephalitis. Studies on Experimental Transmission, Pub Health Rep **48** 1341 (Nov. 3) 1933.

5 Webster, L. T., and Fite, G. L. Virus Encountered in the Study of Material from Cases of Encephalitis in St. Louis and Kansas City Epidemics of 1933, Science **78** 463 (Nov. 17) 1933.

6 Webster, L. T., and Fite, G. L. Proc Soc Exper Biol & Med **31** 344 (Dec.) 1933. Muckenfuss, R. S. Bull New York Acad Med **10** 444 (July) 1934. Muckenfuss, R. S., Armstrong, C., and Webster, L. T. Etiology of the 1933 Epidemic of Encephalitis, J. A. M. A **103** 731 (Sept. 8) 1934. Wooley, J. G., and Armstrong, C. Pub Health Rep **49** 1495, 1934. Webster and Fite<sup>5</sup>.

7 Smadel, J. E., and Moore, E. Am J Path **10** 827, 1934.

8 von Weisner. Wien klin Wchnschr **30** 933, 1917.

monkey with material from the brain of the patient in one of the first cases described by von Economo<sup>9</sup> and produced an acute illness after an incubation period of only a few hours, with death in two days. From the brain of this monkey he recovered a diplostreptococcus, which on subsequent inoculation into another monkey produced a somewhat similar disease. Although the acute course of the experimental infection in the monkeys was unlike the clinical picture characteristic of epidemic (lethargic) encephalitis of von Economo in human beings, von Wiesner nevertheless considered the streptococci to be the probable cause of the disease in human beings.

A considerable number of other authors have reported the isolation of streptococci from the spinal fluid, ventricular fluid or brain substance and occasionally from the blood of human patients, as well as from the brains of experimentally inoculated animals. Among the more important papers mentioning the finding of streptococci are those of Stafford,<sup>10</sup> Morse and Crump,<sup>11</sup> House,<sup>12</sup> Cohn and Lauber,<sup>13</sup> Brasher, Caldwell and Coombe,<sup>14</sup> Bernhardt and Simons,<sup>15</sup> Reichert,<sup>16</sup> Siegmund<sup>17</sup> and others.<sup>18</sup> In view of a certain degree of similarity in clinical and epidemiologic features between the outbreak in Japan in 1924 and that in St. Louis in 1933, it is of special interest to note that several of the Japanese investigators occasionally isolated diplococci or streptococci from their patients, as stated in the review by Kaneko and Aoki.<sup>19</sup>

A survey of the literature reveals that diplococci or streptococci have been encountered more frequently than any other kind of cultivable bacteria in materials from patients with encephalitis presumably containing the etiologic agent of the disease. However, isolation of these organisms directly from the human brain or spinal fluid or from animals inoculated experimentally with these materials has succeeded only occasionally and without regularity. Furthermore, in the hands of most workers, attempts to reproduce the disease in animals by the injection of cultures of streptococci isolated from these sources have led to

9 von Economo, C. *Wien klin Wchnschr* **30** 581, 1917

10 Stafford, C. M. *J Lab & Clin Med* **4** 691, 1919

11 Morse, P. F., and Crump, C. S. *J Lab & Clin Med* **5** 275, 1920

12 House, W. *Epidemic (Lethargic) Encephalitis*, *J A M A* **74** 884 (Feb 7) 1920

13 Cohn, W., and Lauber, I. *Munchen med Wchnschr* **67** 688, 1920

14 Brasher, C. W. J., Caldwell, J. R., and Coombe, E. J. *Brit M J* **1** 733, 1919

15 Bernhardt and Simons. *Neurol Centralbl* **38** 705, 1919

16 Reichert. *Centralbl f Bakt* **85** 261, 1920

17 Siegmund. *Berl klin Wchnschr* **57** 509, 1920

18 Additional references will be found in the report of the Mathewson Commission on Epidemic Encephalitis<sup>3f</sup> and in the paper by Rosenow and Jackson.<sup>20</sup>

19 Kaneko and Aoki. *Ergebn d inn Med u Kinderh* **34** 342, 1928

negative or inconclusive results. For these reasons very few authors have regarded the streptococci as the primary cause of encephalitis, the majority have considered them as secondary invaders or contaminants.

The principal evidence suggesting the primary importance of the streptococcus in the etiology of encephalitis has been brought forward in the extensive studies of Rosenow and his collaborators, and these experiments stand apart from all those before mentioned. In this work strains of green colony streptococci having apparently distinct neurotropic properties were repeatedly isolated directly from material from human beings as well as from experimentally infected animals during the study of various outbreaks of epidemic encephalitis, including the St. Louis epidemic of 1933. Furthermore, the symptoms and pathologic changes produced in rabbits by inoculation with these streptococci were identified by Rosenow with those characteristic of epidemic encephalitis in human beings. Throughout his studies Rosenow used a particular kind of culture medium (dextrose-brain broth) because of its selective effect in favoring the growth of streptococci. He also followed certain technical procedures not commonly employed by other bacteriologists and attributed his success largely to the efficiency of his methods.

*Earlier Studies of Rosenow*—In an early report Rosenow<sup>20</sup> stated that pleomorphic diplococci or streptococci were found on microscopic examination in or near the lesions in sections of the brain and medulla from each of a group of twenty-one patients with encephalitis, whereas these organisms were absent in tissues free from pathologic changes and in sections from the brains of persons dying of other disease which he examined as controls. In several of his later communications similar findings have been reported.

Even with the use of his selective medium, however, Rosenow, like other investigators, has succeeded in the cultivation of streptococci directly from the brains or spinal fluid of only a small proportion of the patients he has studied. Furthermore, in only rare instances has he produced illness in rabbits by direct intracerebral inoculation of the material from the brain or spinal fluid from patients with encephalitis, and in all these cases the experimental disease in the rabbits was evidently due to the streptococci, which were readily cultivated from the brains of the animals after death.

The bulk of Rosenow's studies have begun with streptococci obtained, not directly from the infected tissues of the human brain, but from the nasopharynx, tonsils or similar "atria of infection." On the assumption that these areas, in patients suffering from any of the various clinical forms of epidemic encephalitis, would harbor the specific neuro-

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20 Rosenow, E. C., and Jackson, G. H., Jr. *J. Infect. Dis.* 32: 144, 1923.

tropic streptococci responsible for the disease, Rosenow inoculated rabbits with the original suspension of swabbings from these areas or with primary cultures in dextrose-brain broth. He found that intravenous inoculation of the original mixture of bacteria did not result constantly in localization of streptococci in the brain. However, when these suspensions, or cultures obtained from them, were inoculated intracerebrally in small doses, a culture containing only green colony streptococci was usually obtained from the brains of the animals after death, while the blood from the heart was nearly always sterile. Impressed by these findings, Rosenow concluded that inoculation of the original mixtures into the brain of the living animal served like a culture on an agar plate for the separation of neurotropic strains of green colony streptococci.<sup>21</sup>

Furthermore, when the rabbits were inoculated intracerebrally with nasopharyngeal washings or with the mixed primary cultures of these secured from patients with epidemic hiccup<sup>22</sup> or respiratory arrhythmias<sup>23</sup> (conditions which he thought to have the same cause as encephalitis), spasms of the diaphragm or respiratory disturbances, respectively, developed in a certain proportion of the animals, and these symptoms were more pronounced and were observed more frequently by Rosenow in these animals than in rabbits similarly inoculated with material from other sources.

Likewise, in the several hundred rabbits inoculated by Rosenow intracerebrally with similar cultures from patients with conditions definitely diagnosed as encephalitis,<sup>24</sup> the symptoms in the animals were regarded as a reproduction of the lethargic, parkinsonian, myoclonic or meningeal type of encephalitis, corresponding to the form of the disease in the patients from whom the cultures were obtained. He called attention to the fact that in most of the control rabbits receiving inoculations of nasopharyngeal cultures from normal persons there also developed symptoms referable to the central nervous system, but these symptoms, as a rule, were less severe. Thus, of five hundred and nineteen rabbits inoculated with material from eighty-one patients with encephalitis, 74 per cent died, while of one hundred and six rabbits receiving material from normal persons, only 23 per cent died. In both groups of animals most of the deaths occurred within three days after the inoculation.

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21 Rosenow, E. C. *J Infect Dis* **32** 41 and 72, 1923.

22 Rosenow, E. C. Diaphragmatic Spasms in Animals Produced with a Streptococcus from Epidemic Hiccup, *J A M A* **76** 1745 (June 18) 1921.  
Rosenow<sup>21</sup>

23 Rosenow, E. C. Experiments on the Etiology of Respiratory Arrhythmia Following Epidemic Encephalitis, *Arch Neurol & Psychiat* **11** 155 (Feb.) 1924.

24 Rosenow, E. C. (a) Etiology of Encephalitis, *J A M A* **79** 443 (Aug 5) 1922, (b) *J Infect Dis* **34** 329, 1924.

With some of the cultures of streptococci recovered from the brains of the rabbits after the original inoculation of the unpurified primary cultures, it was possible to reproduce in a series of rabbits practically the same train of symptoms shown by the first animal, but more often the character of the symptoms gradually changed on repeated passage in animals, as a result, according to Rosenow, of a change in the "specific localizing power" of the micro-organism.<sup>25</sup> This change was especially marked in prolonged cultivation on ordinary mediums but could be somewhat minimized if the cultures were transferred in dextrose-brain broth at frequent intervals (from 4 to 6 times each twenty-four hours)

The pathologic changes in the inoculated rabbits were found to vary considerably according to the rapidity with which death followed the inoculation. Usually, in animals that died a week or longer after the injection, the gross appearance of the brain was normal. In the animals dying earlier there were visible a marked congestion of cerebral vessels, "occasional slight general clouding of the meninges, localized infiltration of the pia over the anterior aspect of the midbrain, pons and medulla, associated with slightly or moderately turbid cerebrospinal fluid, small subpial hemorrhages, especially of the medulla and pons, more rarely of the cord and cerebral cortex, rarely a lesion at the point of inoculation, and a variable degree of hemorrhagic edema of the lungs and cloudy swelling of other viscera. Suppurative meningitis, when present, was almost always due to some organism (usually hemolytic streptococcus or staphylococcus) other than the green-producing streptococcus."<sup>26</sup>

Microscopic examination of the brains of animals dying in five days or earlier (i.e., the great majority of the rabbits) showed "leukocytic and round cell infiltration of the pia," focal hemorrhages in the brain and the medulla, often perivascular, associated with a variable degree of cellular infiltration and areas of similar infiltration without hemorrhage. It appears that a considerable proportion of the animals showed a frank purulent meningitis in addition to any other lesions. This meningeal involvement was noted by Rosenow particularly in those animals inoculated with a strain of streptococcus which had gone through a series of rapid passages in animals. In general, the early reaction (in animals dying before the sixth day), which consisted of "a variable degree of leukocytic and round cell infiltration in the meninges and elsewhere," did not differ from the response observed in rabbits inoculated with material obtained from normal persons. However, in animals surviving six days or more, round cells rather than polymorphonuclear

25 Rosenow, E. C. *J. Infect. Dis.* **33**: 531, 1923.

26 Rosenow,<sup>24b</sup> p. 367.



leukocytes tended to predominate, especially in perivascular infiltrations in the depths of the brain. This "characteristic round cell infiltration" was usually lacking in rabbits inoculated with material from normal persons.<sup>27</sup>

As to the characteristics of the streptococci isolated from the patients with encephalitis, Rosenow described them as "somewhat peculiar" pleomorphic organisms, usually producing green colonies on blood agar. A few strains were found to be soluble in bile, but the majority would be classified as *Streptococcus viridans*. The variable morphology of the organisms as seen in tissues and in cultures was stressed, and this pleomorphism was thought to be correlated with the apparent filtrability of certain strains. This property of filtrability was regarded by Rosenow as definitely established, since filtrates of cultures and of other materials sometimes produced the usual symptoms when inoculated intracerebrally into rabbits. However, he stated that in cases in which filtrates were capable of eliciting symptoms of any kind streptococci of normal morphology could be cultivated either from the filtrate itself or at least from the brain of the rabbit after death.<sup>28</sup> As previously stated, the streptococci from patients with encephalitis exhibited a marked tendency to localize in the nerve tissues, and some experiments indicated to Rosenow that this localization might be determined, in part at least, by the production of a "specific poison."<sup>29</sup> Since these streptococci appeared to resemble those found in the normal human respiratory tract, Rosenow conceived their specific neurotropic properties to be temporarily acquired as "a phase, perhaps, in the life cycle of the streptococcic group of organisms."<sup>30</sup>

More recently, Rosenow reported that the specific streptococci of encephalitis could, as a rule, be differentiated from strains occurring in normal throats on the basis of their average cataphoretic velocity.<sup>31</sup> As a result of a great number of determinations of the cataphoretic velocity of the organisms in primary, unpurified dextrose-brain broth cultures from the nasopharynxes of patients with encephalitis and of other persons, and of the velocities shown by cultures of streptococci recovered from the brains of inoculated rabbits after death, Rosenow concluded that the average cataphoretic velocity of streptococci of a

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27 Rosenow,<sup>24b</sup> p. 368

28 Rosenow,<sup>24b</sup> p. 380

29 Rosenow, E. C. Localization in Animals of *Streptococcus* from Cases of Epidemic Hiccup, Encephalitis, Spasmodic Torticollis and Chorea, *Arch. Neurol. & Psychiat.* **19**: 424 (March) 1928.

30 Rosenow, E. C. Specificity of Streptococci in the Etiology of Diseases of the Nervous System, *J. A. M. A.* **82**: 449 (Feb. 9) 1924.

31 Rosenow, E. C., and Jensen, L. B. *J. Infect. Dis.* **52**: 167, 1933.

particular strain is a characteristic definitely correlated with the source and elective localizing capacity of that strain

Thus, under the set experimental conditions of observation he found that both the primary and the passage cultures of streptococci originating from patients with encephalitis required on the average about 4 seconds to traverse the standard distance of 50 microns in the electric field<sup>31</sup> This same range of cataphoretic velocities was shown by other "neurotrophic" strains of streptococci recovered by Rosenow, from patients with other diseases of the nervous system, such as those obtained from patients with poliomyelitis<sup>32</sup> In contrast, streptococci from the throats of normal persons had a higher cataphoretic velocity, showing under the same experimental conditions a cataphoretic time of only about 3 seconds On the other hand, strains of streptococci originating from persons afflicted with diseases other than those involving the nervous system showed an average cataphoretic velocity different from that of organisms from either normal subjects or persons with encephalitis Those from patients with influenza, for example, had an average cataphoretic time of from 4.5 to 5 seconds<sup>33</sup> Repeated determinations showed, however, that strains which had a particular average velocity when originally secured did not always maintain this characteristic unchanged on further artificial cultivation or after passage in animals

Rosenow stated further that streptococci originating from patients with encephalitis differed from those derived from normal persons in their immunologic properties also Antistreptococcus serums prepared by hyperimmunizing horses with a mixture of strains of streptococci obtained by Rosenow in his earlier work with encephalitis (1923) and with poliomyelitis were found to agglutinate the streptococci isolated during subsequent study of various outbreaks of encephalitis, and this agglutination reaction was regarded as specific for the "encephalitis" streptococcus He stated "When agglutination of a particular strain was more marked, and when it occurred in higher dilutions in the encephalitis and poliomyelitis hyperimmune serums than in the type pneumococcus serums, immune streptococcus serum from influenza, and normal horse serum, it was considered specific agglutination"<sup>34</sup> He noted that the agglutinability of different strains from patients with encephalitis varied greatly, and only rarely was the titer high

Though agglutination tests with the serums obtained from patients convalescing from encephalitis during studies of various outbreaks of the disease never gave consistent results, their agglutinating power for typical strains of streptococci producing encephalitis was weak at best,

32 Rosenow, E C J Infect Dis 50 377, 1932

33 Rosenow, E C J Infect Dis 54 91, 1934

34 Rosenow,<sup>24b</sup> p 385

Rosenow nevertheless considered the results as indicative of a definite, though feeble, specific reactivity<sup>30</sup>

He found, furthermore, that his encephalitis antistreptococcus serum had some protective power for rabbits inoculated with streptococci isolated from patients with encephalitis, and consequently this serum was early recommended by Rosenow for use in treatment of human patients with encephalitis<sup>35</sup>

*Reports of Other Investigators*—Observations which might be regarded as offering direct support of Rosenow's views were made by Evans and Freeman in 1926. With nasal washings and with cultures of streptococci recovered from the blood and the mesencephalon of a patient dying of encephalitis these authors produced a rapidly fatal meningo-encephalitis in rabbits and in monkeys. Filtrates of cultures and of the emulsions of brains of human beings and of animals proved harmless, but when such filtrates were planted in a meat medium, streptococci could later be recovered from this medium. These findings indicated to the authors that the streptococci must have existed in filtrable form in the original material from the brain. In some of the cultures inoculated with emulsions of human brain they found not only streptococci, but also diphtheroids and spore-forming bacilli. They suggested that these bacteria, as well as the streptococci, were only the visible forms of an invisible, filtrable virus of encephalitis<sup>36</sup> (Evans has more recently described in some detail her views on this "metamorphosis" of streptococci into spore-bearing rods and further into filtrable forms<sup>37</sup>). Freeman<sup>38</sup> cultivated streptococci from several other patients with encephalitis, and Evans<sup>39</sup> cultured these organisms from six samples of material containing the virus of herpes.

On the other hand, Olitsky and Long,<sup>40</sup> using Evans' technic, were unable to find any connection between the virus of herpes and streptococci, and Tang and Ruiz Castaneda,<sup>41</sup> after a similar study, concluded that visible organisms, including streptococci, which may occasionally be cultivated from samples of viruses producing encephalitis in rabbits are secondary invaders or accidental contaminants and have nothing to do with the viruses themselves. The same conclusion was reached by

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35 Rosenow, E. C. Specific Serum Treatment of Epidemic (Lethargic) Encephalitis. Further Results, *J. A. M. A.* **80** 1583 (June 2) 1923.

36 Evans, A. C., and Freeman, W. *Pub. Health Rep.* **41** 1095, 1926.

37 Evans, A. C. *Pub. Health Rep.* **47** 1723, 1932.

38 Freeman, W. Chronic Epidemic Encephalitis, *J. A. M. A.* **87** 1601 (Nov 13) 1926, Encephalitis with Tumor of the Brain, *Arch. Neurol. & Psychiat.* **18** 433 (Sept.) 1927, *J. Nerv. & Ment. Dis.* **65** 171, 1927.

39 Evans, A. C. *Pub. Health Rep.* **42** 171, 1927.

40 Olitsky, P. K., and Long, P. H. *J. Exper. Med.* **48** 199, 1928.

41 Tang, F. F., and Ruiz Castaneda, M. *J. Bact.* **16** 431, 1928.

McKinley and Douglass<sup>42</sup> in connection with their studies of herpes encephalitis in cebus monkeys

McKinley<sup>43</sup> stated that by following Rosenow's technic in all details he succeeded in producing a fatal meningo-encephalitis in rabbits by intracerebral inoculation of nasopharyngeal cultures from a high proportion (80 per cent) of a group of healthy persons in Puerto Rico. Furthermore, in his opinion, the symptoms and pathologic changes in these rabbits were the same as those in rabbits similarly inoculated by Rosenow with cultures from patients with encephalitis and demonstrated to him in Rosenow's laboratory. So far as we are aware, this is the only study of encephalitis aside from our own which was conducted exactly according to Rosenow's technic.

*Rosenow's Findings in St. Louis*—Employing the same methods of experimental study and the same technical procedures which he had followed in the past, Rosenow investigated cases of encephalitis in St. Louis during the height of the epidemic of 1933. His principal findings<sup>44</sup> were in all essentials similar to those obtained by him in the earlier studies reviewed in this paper. He demonstrated either by direct microscopic examination or by culture in dextrose-brain broth, the presence of streptococci in the specimens of spinal fluid, blood and glycerinated brain from several patients with encephalitis in St. Louis, and he stated that all the strains isolated from these sources exhibited a characteristic velocity in the electric field and were virulent when inoculated into rabbits. The organisms in 81 per cent of the primary dextrose-brain broth cultures of material from the nasopharynx of sixty-four persons suffering from acute encephalitis were found to have "mainly neurotropic cataphoretic velocity" (i. e., a cataphoretic time of from 3.5 to 4 seconds), whereas only 52 per cent of the cultures from one hundred and forty-nine well persons or from persons with diseases other than encephalitis residing in the epidemic zone and 28 per cent of an equal number of cultures from persons without encephalitis living remote from the epidemic showed a similar range of cataphoretic velocities.

Intracerebral inoculation into a large series of rabbits of streptococci from primary brain broth cultures of material from the nasopharynx or from the spinal fluid of the patients with encephalitis, or of purified cultures of streptococci from these sources, produced in the rabbits an acute and usually rapidly fatal illness, and in Rosenow's

42 McKinley, E. B., and Douglass, M. J. *Infect Dis* **47** 511, 1930.

43 McKinley, E. B. *Proc Soc Exper Biol & Med* **27** 436, 1930.

44 Rosenow, E. C. *Proc Staff Meet, Mayo Clin* **8** 559 (Sept 13) 1933, *Weekly Bull St Louis M Soc* **28** 69 (Oct 13) 1933, *Proc Soc Exper Biol & Med* **31** 785 (Nov) 1933.

opinion these animals showed "the more important clinical and pathologic manifestations" of encephalitis as seen in the human patients in St. Louis. On the other hand, cultures from the nasopharynges of normal persons, inoculated in the same way, caused symptoms and death in a smaller proportion of rabbits, and the lesions were considered to be "less marked."

Rosenow's "encephalitis antistreptococcus serum" was found to agglutinate "markedly and in high dilution" most of the strains of streptococci obtained by him from patients with encephalitis and also partially protected rabbits when mixed with the streptococci before inoculation. It was stated that the serum of convalescent patients with encephalitis in St. Louis agglutinated specifically and slowed the cataphoresis of the "more sensitive" strains of streptococci isolated from patients with typical manifestations.

#### METHODS

As indicated, we endeavored to follow as closely as possible the technical procedures described and personally demonstrated to us by Dr. Rosenow. The methods employed in the work reported in this communication are outlined in the following paragraphs.

*Selective Medium*—Dextrose-brain broth medium was prepared by placing in tall, narrow tubes (20 cm. by 1.5 cm.) small pieces of fresh washed calf brains to a depth of about 2½ inches (6.3 cm.) and adding dextrose broth in sufficient amount to make the tube about three-fourths full. The broth was prepared with 10 Gm. of Bacto peptone, 5 Gm. of sodium chloride, 2 Gm. of chemically pure dextrose and 10 cc. of Andrade's indicator per liter and adjusted to pH 7.4. A small amount of calcium carbonate (powder) was added to each of the tubes before they were placed in the autoclave for twenty minutes at a pressure of 15 pounds (6,803 Gm.).

*Cultures from the Nasopharynx*—Material for these cultures was secured by passing a small sterile cotton swab on the end of an aluminum wire, bent at a suitable angle, over the nasopharynx while the throat was illuminated with a small flash-light to which the tongue depressor was attached. By this method satisfactory swabbings from an area limited strictly to the nasopharyngeal region were secured with the greatest ease. The organisms adhering to the swab were thoroughly emulsified in 2 cc. of warm, sterile Locke's solution containing 0.2 per cent gelatin, and the resulting emulsion together with the swab was placed for one hour in the incubator. The emulsion was then inoculated into a tube of warm dextrose-brain broth and also streaked on two warm hormone rabbit blood agar plates by means of the original swab. At first additional blood agar plates were streaked and incubated anaerobically,<sup>45</sup> but this was soon abandoned, since no additional information was gained thereby.

Smears stained by Gram's method were prepared from the twelve to twenty-four hour dextrose-brain cultures, and careful records were kept of the morphology of the organisms. The primary blood agar plates were examined, the amount and character of the growth were recorded, and smears were usually made from several representative colonies.

*Determinations of Cataphoretic Velocity*—In order to learn the details of the procedure and apparatus used by Dr Rosenow for the determination of cataphoretic velocity, one of us visited his laboratory at Rochester, Minn. There, the method of making determinations was practiced until in a series of parallel tests on a number of different cultures quantitative results were regularly obtained agreeing within less than 1 per cent with those of the worker charged with these determinations in Dr Rosenow's laboratory. An apparatus similar in every essential respect to that employed by Rosenow<sup>32</sup> was set up in our laboratory.

Material for the tests was secured by removing 2 or 3 cc of the liquid portion of the dextrose-brain broth cultures into chemically clean test tubes, numbered serially. These tubes were centrifugated at 1,400 revolutions per minute for ten minutes, the supernatant broth was then thoroughly drained off, and the sedimented organisms were suspended in approximately 17 cc of distilled water. Readings on these suspensions were usually made at once, and in no case was the examination delayed for more than two hours. Each suspension in distilled water, after a thorough shaking, was introduced into a Northrop-Kunitz-Mudd cataphoresis apparatus, and the time required (in seconds and quarter-seconds) for each of from twenty to twenty-five organisms in the suspension to traverse the unit distance of 50 microns was determined by a stop-watch.<sup>46</sup>

The accuracy of the determinations was controlled in several ways. The drop in voltage between the platinum electrodes was determined by direct readings just before and just after performance of the tests on a group of cultures and was found to vary in the course of the determinations not more than  $\pm 1.5$  per cent. This variation was considered as a limit of error of the method. At different times between individual determinations the cataphoretic time of the particles of Lloyd's reagent was measured, and the readings on the cultures were not considered valid unless those on Lloyd's reagent showed an average time of approximately 4.5 seconds. All the measurements of cataphoretic velocity were made by the same person, who at the time had no knowledge of the source of the cultures. In nearly every group of cultures tested at one time, one or more samples were submitted for examination in duplicate as a further means of checking the accuracy of the readings.

#### INCIDENCE OF STREPTOCOCCI IN CULTURES FROM PATIENTS WITH ENCEPHALITIS AND FROM NORMAL CONTROLS

*Cultures from the Brain, Spinal Fluid and Blood of Patients with Encephalitis*—We did not undertake a systematic bacteriologic study of specimens of brain, spinal fluid or blood, but a few samples of these

46 The average of these readings on a particular culture gives the average cataphoretic time of the organisms in that culture. The average cataphoretic velocity is expressed in terms of microns per second, volts per centimeter, according to the formula

Cataphoretic velocity =  $\frac{\text{standard distance traversed (50 microns)}}{\text{time in seconds}} \times \frac{\text{distance between platinum electrodes}}{\text{total voltage drop}}$  Thus, in our apparatus, with the platinum electrodes 3.58 cm apart and the voltage drop between them 29.5 volts, an organism with an average cataphoretic time of four seconds has a velocity expressed as 1.52 CV =  $\frac{50 \times 3.58}{4 \times 29.5} = 1.52$  (charts 1 and 2)

materials were cultured, most of them prior to the beginning of any experimental work. On ordinary mediums of several kinds (including cooked meat medium but not including dextrose-brain broth) cultures were made from specimens of the fresh brain and of glycerinated emulsions of brain from sixteen different patients with encephalitis. No growth appeared in any case in the mediums inoculated with the specimens of fresh brain. The glycerinated emulsions of brain, however, were found to contain a few bacteria in several cases, but these were of diverse kinds, mostly diphtheroids and staphylococci, and streptococci were observed in cultures from only two specimens, in each of which these organisms were accompanied by diphtheroids. Cultures of blood from fifteen patients with encephalitis made in ordinary infusion broth were all sterile, except one in which a large gram-positive bacillus, evidently a contamination, was found. No growth developed in cultures inoculated with specimens of spinal fluid from seventeen different patients, except in a single instance, when a mixed growth of an unidentified gram-amphophilic coccus and a gram-negative bacillus appeared.

After we began the use of Rosenow's dextrose-brain broth, we were able to make only a very few additional cultures because of the pressure of other work. Three samples of spinal fluid and two of blood from patients suffering from acute encephalitis were inoculated (a few hours after their collection) in amounts of 1 cc. or more into warm dextrose-brain broth. Only three of the five cultures ever showed any evidence of growth, and in each of these instances only a sporulating gram-positive bacillus was present.

In a single instance, however, green colony streptococci were recovered from the brain of an elderly patient who died of encephalitis. At the autopsy, conducted about twelve hours after death, ventricular fluid was collected with a pipet immediately after the skull was opened, and 1 cc. of this fluid was introduced into a tube of warm dextrose-brain broth. No growth was evident in this culture after twenty-four hours' incubation, but a transplant into another tube of brain broth medium made at that time showed turbidity in twelve hours, and a similar growth had developed by that time in the original tube. This growth was found to consist of an apparently pure culture of green colony streptococci. This particular strain was designated H Br-1, and because of its origin it was included in the studies to be described later, which otherwise dealt entirely with cultures derived from the nasopharynx.

*Cultures from the Nasopharynxes of Patients with Encephalitis and of Normal Persons*—Cultures of material from the nasopharynx were obtained from twenty-nine patients at the St. Louis Isolation Hospital. Twenty-one of these patients were suffering from typical acute encephalitis of from two to nine days' duration at the time the cultures were

taken Of the remaining eight patients, five were convalescing from an acute attack of this disease which had occurred from three to six weeks previously, and three had only mild and questionable symptoms of from seven to ten days' duration

As controls, cultures of material from the nasopharynx were made during the period of the epidemic from twelve normal persons residing in St Louis and, in addition, from nine well persons residing at a considerable distance from the area involved in the epidemic (Washington, D C) The swabbings from the latter persons were secured at our request through the kindness of Dr Leake and were brought by him to St Louis, where they were inoculated into culture mediums in the usual way within less than twenty-four hours after they were collected

The primary blood agar plate cultures inoculated directly with the swabbings from the nasopharynxes of twenty-five of the twenty-nine patients with encephalitis (86 per cent) showed the presence of colonies of streptococci causing the alpha type of hemolysis As may be seen in table 1, the relative number of these green colony streptococci appeared to be consistently higher in those cultures secured from acutely ill patients than in those from mildly ill or convalescent patients Colonies of the green-producing streptococci apparently predominated in the blood agar plates from about one half of all the patients, and they occurred in almost pure culture in two instances In addition to streptococci, many colonies of staphylococci, often of the hemolytic variety, were present in most of the blood agar plates A smaller number of colonies of the several other kinds of bacteria normally present in the nasopharynx (especially gram-negative diplococci and diphtheroids) were also observed Colonies of influenza bacilli were encountered in one instance only Hemolytic streptococci were noticeably absent

The primary cultures of material from the nasopharynx on blood agar from sixteen (76 per cent) of the twenty-one normal persons contained streptococcus colonies of the green type accompanied by a variable number of colonies of other bacteria commonly found in the nasopharynx (table 1) Among these cultures, one set of plates inoculated with material from a student in St Louis, who was perfectly well and had not had any known contact with patients with encephalitis, yielded practically a pure growth of green-producing streptococci These organisms appeared to be predominant in one third of the blood agar cultures from twelve normal persons in St Louis and in an even larger proportion (56 per cent) of those made from nine healthy residents of Washington, D C The cultures from the latter source differed from those made from normal persons in St Louis in that they contained a greater variety of bacteria, but the green colony streptococci were nevertheless relatively numerous



Thus, while the number of these primary nasopharyngeal cultures observed is insufficient to permit any very definite conclusions, it appears that the blood agar cultures from the nasopharynges of the acutely ill patients with encephalitis showed a slightly greater incidence of green colony streptococci and a somewhat less varied flora than did similar cultures from normal controls. This relative uniformity of the flora was especially marked in comparison with the variety of different organisms present in the cultures from normal persons living in Washington, D. C.

The primary cultures from the nasopharynx in dextrose-brain broth, whether from the patients with encephalitis or from the normal persons, always showed, in smears, a marked predominance of gram-positive

TABLE 1—*Relative Abundance of Streptococci in Primary Blood Agar Cultures from the Nasopharynx*

Source of Cultures	Total Cul- tures	Green Colony Streptococci			Staphylococci		Other Organisms	
		Many	Few	None	Many	Few	Many	Few
Acute encephalitis cases from 2 to 10 days after onset	21	13	4	4	5	12	0	15
Percentage		62	19	19	24	57	0	71
Mild encephalitis and convalescent cases	8	1	7	0	4	2	0	8
Percentage		13	87	0	50	25	0	100
Total encephalitis cases	29	25	4		23		23	
Percentage		86	14		79		79	
Normal persons in St. Louis	12	4	4	4	6	1	2	6
Percentage		33.3	33.3	33.3	50	8	17	50
Normal persons in Washington, D. C.	9	5	3	1	2	6	2	5
Percentage		56	33	11	22	67	22	56
Total normal persons	21	16	5		15		15	
Percentage		76	24		71		71	

diplococci and streptococci. Apparently owing to the selective effect of this medium, gram-negative organisms never developed, and on microscopic examination the growth appeared to consist almost entirely of gram-positive cocci, with occasional diphtheroid bacilli.

However, the cocci present in most of these primary cultures were not all streptococci by any means. Subcultures on blood agar plates showed that the growth in the brain broth cultures consisted in nearly every instance of a mixture of organisms similar to that appearing on the primary blood agar plates from the same source, except that there was usually a relatively more abundant development of the gram-positive cocci. Green colony streptococci appeared to be predominant in about the same proportion of these primary brain broth cultures from the patients with encephalitis and from the normal controls as they were in the corresponding primary blood agar plates from the same persons. In the case of the two patients with acute encephalitis and of one normal

person in St. Louis previously mentioned, the primary blood agar plates inoculated with material from the nasopharynx showed an apparently pure growth of green colony streptococci, and the brain broth cultures likewise contained the streptococci only. In all the other instances, however, a mixture of organisms developed, consisting of a variable number of staphylococci in addition to the streptococci, and often of other gram-positive cocci and diphtheroids as well.

#### PROPERTIES OF STREPTOCOCCI ISOLATED

*Determinations of Cataphoretic Velocity*—All the primary dextrose-brain broth cultures made from the nasopharynges of patients with encephalitis and of normal persons, as well as the passage cultures of streptococci recovered at different times from inoculated animals, were tested to determine the cataphoretic velocity of the organisms. For comparison with our own strains we also tested repeatedly various subcultures of the strain used by Dr. Rosenow for demonstration in our laboratory and, in addition, five other strains isolated by him which he later sent us as examples of typical "encephalitis" streptococci. Determinations of cataphoretic velocity were frequently made on different subcultures of the same strain of streptococci, while it was being maintained by three or four transfers per day in the brain broth medium.

In general we could not discover any consistent correlation between the cataphoretic velocity and either the source or the relative virulence of the organisms when inoculated into rabbits.

Our findings on the cataphoretic velocity of the organisms in the primary cultures in dextrose-brain broth are presented graphically in chart 1. The data included in this chart were tabulated in the manner employed by Rosenow in his reports. The percentages shown are not based on the average cataphoretic time of the bacteria in individual cultures but represent the proportion of all the individual organisms in each group of cultures from a given source which had a particular cataphoretic time. We found no preponderance of organisms having a "neurotropic" velocity (i. e., a cataphoretic time of 4 seconds) in the primary cultures from patients with encephalitis. On the contrary, the group of cultures from normal persons, more than half of whom resided in a city remote from the area affected by the epidemic, had a somewhat higher proportion of organisms approaching this velocity.

Despite this failure of most of the primary cultures of material from the nasopharynges of patients with encephalitis to show the cataphoretic time, said by Rosenow to be characteristic of organisms having an elective localizing power for the central nervous system, practically all of them exhibited the expected virulence for rabbits. We were never able to distinguish any consistent differences in the effects produced in rabbits

by the inoculation of cultures containing organisms of different average cataphoretic velocity (Description of the experiments with animals is deferred to the second paper of this series)

The results of determinations of the cataphoretic velocity of organisms in the pure cultures of green colony streptococci obtained after animal passage by us from material from patients with encephalitis or from material from normal persons and of the six strains of "encephalitis" streptococci sent to us by Dr Rosenow are tabulated in chart 2. In all three groups of cultures the highest percentage of organisms traversed the standard distance of 50 microns in less than from 3.5 to 4 seconds, the time neurotropic strains are expected to require, although the great majority of these cultures did produce in rabbits severe illness like that described as characteristic by Rosenow. As in

Source of Cultures	%	Cataphoretic Time and Velocity
Encephalitic Patients in St. Louis	25 20 15 10 5 0	(18,28,583)
Normal Persons in St. Louis and Washington, D. C.	25 20 15 10 5 0	(14,14,297)
Time in Seconds		2.0 3.0 4.0 5.0 6.0
Microns per second Volts per centimeter		3.0 2.0 1.5 1.2 1.0

Chart 1—Cataphoretic time and velocity of organisms in primary cultures of material from the nasopharynxes of patients with encephalitis and of normal persons. The figures in parentheses give the number of strains, the number of separate cultures in each group and the number of readings on which the percentages were based.

the case of the primary cultures (chart 1) we did not observe, on the whole, any significant difference in the average cataphoretic velocity of the bacteria in cultures from different sources, and we noted nothing to indicate that a peculiar velocity is associated with the streptococci of a particular origin or of a particular degree of virulence.

This lack of correlation appeared even more striking when we considered the average cataphoretic time of the organisms in individual cultures of various origins. The figure representing this average was arrived at by averaging the observed time required for from twenty to twenty-five separate organisms of a particular culture to traverse the standard distance of 50 microns.

We found that only one of the six strains selected by Dr Rosenow showed an average cataphoretic time approaching the "neurotropic" range of 4 seconds. This was the strain which will be referred to in subsequent experiments as Ros 3. Even with this strain, however, the readings were not entirely consistent, for in numerous determinations made on subcultures at different times in the course of repeated passages in animals, variations in the cataphoretic time were recorded from about 2 seconds to 5 seconds. None of the other five strains ever showed an average cataphoretic time as great as 3.5 seconds. The strain used by Dr Rosenow in our laboratory to demonstrate pathogenesis in rabbits showed by our tests averages between 2.5 and 3 seconds in repeated determinations.

Source of Culture	%	Cataphoretic Time and Velocity
"Typical" Strains Isolated from Encephalitic Patients by Dr. Rosenow.	25	(6;60,1235)
	20	
	15	
	10	
	5	
	0	
Strains Isolated by us from Encephalitis Patients in St. Louis.	25	(8;89,1809)
	20	
	15	
	10	
	5	
	0	
Strains Isolated by us from Normal Persons in St. Louis and Washington, D. C.	25	(10;36;734)
	20	
	15	
	10	
	5	
	0	
Time in Seconds		2.0 3.0 4.0 5.0 6.0
Microns per second Volts per centimeter		3.0 2.1 1.5 1.2 1.0

Chart 2—Cataphoretic time and velocity of pure cultures of green colony streptococci isolated after passage in animals from patients with encephalitis and from normal persons. The figures in parentheses give the number of strains, the number of cultures in each group and the number of readings on which the percentages were based.

The strain of streptococcus previously referred to, which we isolated from the brain of a patient with encephalitis (strain H Br-1) showed an average cataphoretic time of about 3 seconds in repeated tests made both before and after passage in animals. Another culture of streptococcus, which was isolated by us originally from the brain of a rabbit inoculated intracerebrally with the primary nasopharyngeal culture from a patient severely ill with encephalitis (strain En 29) and which produced in rabbits typical symptoms, also exhibited in the majority of the many subcultures tested a cataphoretic time of only about 3 seconds.

On the other hand, cultures of the strain En 24, which were similarly virulent for rabbits, often showed a cataphoretic time as great as 4 seconds or more. Among the strains of streptococci isolated from the nasopharynges of normal persons, several showed, in repeated tests, an average cataphoretic time as great as that of any of those originating from patients with encephalitis, and most of these were also very virulent for rabbits, while a few, though exhibiting the same average velocity, were distinctly less virulent.

Thus, it can be seen that our findings on the cataphoretic velocity of streptococci from groups of cultures from different sources and on individual cultures of streptococci do not support the contention of Rosenow that a certain narrow range of cataphoretic time (around 4 seconds) is a characteristic peculiar to the virulent streptococci originating from patients with encephalitis.

*Cultural Characteristics*—All the strains of streptococci isolated during this study produced the alpha type of hemolysis on blood agar plates. The colonies were mostly smooth, round disks, but rough-surfaced colonies of the types familiar in stock cultures of streptococci were plentiful in many cultures. In dextrose-brain broth and in serum broth multiplication was rapid and luxuriant, and, with the exception of a very few strains, the growth was uniform and diffuse throughout the medium. After repeated transfers in dextrose-brain broth, a few long-chained strains showed a tendency to spontaneous clumping along the sides and bottom of the tube. Morphologically the organisms appeared as small gram-positive cocci, varying somewhat in size in different cultures and occurring usually in pairs and short chains but occasionally in long chains. They appeared to be no more pleomorphic than is usual for streptococci.

None of the forty-two strains tested were found to be soluble in bile. The fermentation reactions of these strains are summarized in table 2. These reactions and the other properties mentioned appear to be those of *Str. viridans*.

*Agglutination Reactions with Rosenow's Encephalitis Antistreptococcus Serum*—A total of fifty cultures, representing thirty-three different strains of streptococci isolated during this study, were tested for agglutination against the "encephalitis antistreptococcus serum" of Rosenow.

The results are summarized in table 3. It will be seen that all strains, including those from normal persons, were agglutinated by Rosenow's serum, but few in very high dilution. With the exception of strain H Br-1 (from the brain of a patient with encephalitis) and N 26 (from a normal throat), all cultures were agglutinated in a serum dilution at least as high as 1:80 and the great majority in a dilution 1:320. Of

the seventeen strains from patients with encephalitis only two were agglutinated in a dilution of 1 1,280 or higher. Only three of the six strains sent us by Dr. Rosenow were acted on in a dilution beyond 1 80,

TABLE 2—*Fermentation Reactions*

Carbohydrate	Number of Strains Producing Fermentation
Dextrose	42
Lactose	41
Saccharose	42
Maltose	41
Raffinose	39
Salicin	23
Inulin	3
Mannitol	0

TABLE 3—*Agglutination Reactions with Rosenow's Encephalitis Antistreptococcus Serum*

Source of Cultures	Strain		Number of Cul- tures Tested	Number Agglutinated											Con trol
	No	Designa- tion		Serum Dilution, 1											
				20	40	80	160	320	640	1,280	2,560	5,120	10,240		
Patients with enceph- alitis	1	En 14	1	1	1	1	1	1	0	0	0	0	0	0	
	2	En 17	1	1	1	1	1	1	0	0	0	0	0	0	
	3	En 24	1	1	1	1	1	1	0	0	0	0	0	0	
	4	En 41	1	1	1	1	1	1	0	0	0	0	0	0	
	5	En 44	1	1	1	1	1	1	0	0	0	0	0	0	
	6	En 6(Br)	3	3	3	3	3	3	3	1	0	0	0	0	
	7	En 6(Bl)	2	2	2	2	2	1	1	0	0	0	0	0	
	8	En 10	1	1	1	1	1	1	1	0	0	0	0	0	
	9	En 14	2	2	2	2	2	1	1	0	0	0	0	0	
	10	En 16	1	1	1	1	1	1	1	0	0	0	0	0	
	11	En 17	1	1	1	1	1	1	1	1	1	1	1	0	
	12	En 24	2	2	2	2	1	0	0	0	0	0	0	0	
	13	En 28	1	1	1	1	1	0	0	0	0	0	0	0	
	14	En 29	2	2	2	2	2	0	0	0	0	0	0	0	
	15	En 34	1	1	1	1	1	1	1	0	0	0	0	0	
	16	En 15	1	1	1	1	1	1	1	0	0	0	0	0	
	17	H Br 1	1	1	0	0	0	0	0	0	0	0	0	0	
Totals	17		23	23	22	22	21	15	11	4	2	1	1	0	
Rosenow's cultures	1	Ros 1	1	1	1	1	1	1	1	1	0	0	0	0	
	2	Ros 2	3	3	3	3	3	3	3	3	3	2	1	0	
	3	Ros 3	3	3	3	3	3	3	3	3	3	0	0	0	
	4	Ros 4	2	2	2	2	0	0	0	0	0	0	0	0	
	5	Ros 7	2	2	2	2	0	0	0	0	0	0	0	0	
	6	302	1	1	1	1	0	0	0	0	0	0	0	0	
Totals	6		12	12	12	12	7	7	5	4	3	2	1	0	
Normal persons	1	N 17	1	1	1	1	0	0	0	0	0	0	0	0	
	2	N 18	1	1	1	1	0	0	0	0	0	0	0	0	
	3	N 1 Br	1	1	1	1	0	0	0	0	0	0	0	0	
	4	N 10	1	1	1	1	1	0	0	0	0	0	0	0	
	5	N 18	4	4	4	4	3	2	2	2	2	2	1	0	
	6	N 19	1	1	1	1	1	1	0	0	0	0	0	0	
	7	N 22	1	1	1	1	1	0	0	0	0	0	0	0	
	8	N 23	1	1	1	1	1	1	1	0	0	0	0	0	
	9	N 25	3	3	3	3	0	0	0	0	0	0	0	0	
	10	N 26	1	1	0	0	0	0	0	0	0	0	0	0	
Totals	10		15	15	14	14	7	4	3	2	2	2	1	0	

and only one (Ros 3) in a dilution beyond 1 1,280. Among the ten strains from normal throats one (N 18) was as strongly agglutinated as any of the other cultures (1 10,240 dilution). Aside from this strain, however, the organisms from normal persons were somewhat less often

agglutinated in the higher dilutions than the streptococci from patients with encephalitis. At the 1:640 dilution, for example, eleven of twenty-three cultures from persons with encephalitis (48 per cent), were clumped, but only three of fifteen cultures from normal persons (20 per cent) were agglutinated. The difference was obviously slight, however, and it is clear that individual strains varied greatly in agglutinability without regard to their source.

#### SUMMARY AND COMMENT

As a background for the present study a review of the literature bearing on the relationship of streptococci to the etiology of epidemic encephalitis is presented, from which it is clear that the experimental evidence in support of the view that streptococci play the primary rôle in the causation of this disease is to be found almost entirely in the work of Rosenow. In this and in the second communication of this series the results of an independent investigation of this question carried out during the St. Louis epidemic are reported. Throughout the work the special technical procedures used by Rosenow were followed in every detail.

The majority of cultures in ordinary mediums made from the brain tissue, blood or spinal fluid from a group of patients with encephalitis yielded no growth, while in the remaining cases bacteria of diverse kinds, and only rarely streptococci, were encountered. This failure to cultivate streptococci consistently on ordinary mediums from these sources is quite in line with the experience of other workers who have inoculated material of the same kind from patients with epidemic encephalitis without result. A few additional samples of spinal fluid cultured in Rosenow's medium (dextrose-brain broth) also failed to show the presence of streptococci. However, in the only instance in which we had the opportunity to inoculate ventricular fluid from a patient with encephalitis directly into dextrose-brain broth, a pure growth of green colony streptococci developed. After a considerable experience in its use we do not hesitate to agree with Rosenow that the brain broth medium is an unusually favorable one for the cultivation of streptococci from any source. Its wider employment by others would undoubtedly result, as in Rosenow's hands, in the more frequent demonstration of the presence of streptococci in various materials in which they may not be detected by the use of ordinary laboratory mediums.

Blood agar plate cultures from the nasopharynges of patients with encephalitis and of normal persons residing in the epidemic area as well as elsewhere seemed to indicate that there was a definite tendency for green colony streptococci to predominate in the nasopharyngeal flora of the patients acutely ill with encephalitis in St. Louis. In several cases

these organisms occurred either alone or mixed only with staphylococci. However, the cultures from normal persons showed in many instances a similar predominance of streptococci, so that on the whole the nasopharyngeal flora of the patients affected by the epidemic can hardly be regarded as distinctive.

The various strains of streptococci isolated appeared to have no unusual morphologic or cultural properties and would all be placed in the class generally designated as *Str. viridans*. In agglutination reactions with Rosenow's "encephalitis antistreptococcus serum" the strains originating from patients with encephalitis were agglutinated somewhat more often in the higher dilutions than those obtained from normal persons, but all the strains were agglutinated in some degree and individual strains varied greatly in agglutinability irrespective of their source.

Although our measurements of cataphoretic velocity were carefully performed, the same procedures as those employed in Rosenow's laboratory being followed, we did not confirm his findings. We could not discover any consistent correlation between the cataphoretic velocity of the streptococci and their source or their relative virulence for rabbits.

The lack of agreement between our findings and the published data of Rosenow might conceivably be due in part to differences between the medium employed in his laboratory and that used in ours. Only a limited attempt to check this point was made. Early in the course of the study we asked Dr. Rosenow to test the cataphoretic velocity of certain cultures grown in dextrose-brain broth prepared in our laboratory and the velocity of the same cultures when cultivated in parallel in his own brain broth medium. In a personal communication Dr. Rosenow reported that in three of six of these cultures the readings of cataphoretic velocity "paralleled quite accurately in the two mediums." In the remaining cultures he found a greater scattering of the range of velocities, and the organisms appeared to him to be more pleomorphic in our medium than in his own. However, the extent of variation was well within the range of that often observed and reported by Rosenow<sup>47</sup> in different subcultures of the same strains in the same medium.

From our admittedly limited experience we judge that there are two factors not mentioned by Rosenow which appear to have considerable influence on the results of determinations of cataphoretic velocity on cultures of the kind under discussion. These are (1) the presence of bacteria other than streptococci in most of the primary cultures and (2) the tendency of some but not all strains of streptococci to form relatively long chains when subcultured repeatedly, at intervals of a few hours (according to Rosenow's technic), in dextrose-brain broth.

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47 Rosenow<sup>32, 33</sup>



With respect to readings of cataphoretic velocity on the primary dextrose-brain broth cultures from the nasopharynx, the fact that these cultures almost always contain a mixture of organisms does not seem to have been given sufficient consideration. Unless one is willing to assume that every organism in these cultures is a form of pleomorphic streptococcus, it must be realized that many of the individual bacteria for which the cataphoretic time is being measured may not be streptococci at all. In consideration of this point, we believe that, in general, determinations of cataphoretic velocity on such unpurified primary cultures from the nasopharynx are of limited significance. Of course, since these cultures usually contain mainly streptococci, the greater the quantity of data the less weight this objection would have.

On repeated determinations of the cataphoretic velocity of the pure streptococci in different subcultures of the same strain at different times we noted that usually a gradual reduction in the average velocity (i e, an increase in the cataphoretic time) occurred as the subcultures were carried through the routine, often repeated (from 4 to 6 times per day) transfers in the brain medium. With some strains the average velocity became markedly slower after several transplants, whereas with other strains the change was slight. In our experience the strains of streptococci which most frequently showed a cataphoretic time approaching an average of 4 seconds or more were the same strains that most regularly developed especially long chains after many frequently repeated transfers in dextrose-brain broth. We observed on several occasions that if one makes the determination of cataphoretic velocity in the routine way on a suspension of one of these cultures containing many long chains without attempting to avoid the formation of chains, the average cataphoretic time of the culture is always high (5 or 6 seconds or more), whereas if in making the readings one takes especial effort to avoid timing of the chained elements, the same suspension may give an average of only about 3 seconds or less. Since the routine procedure does not afford any adequate control over this factor, it seems doubtful whether figures on the cataphoretic velocity of streptococci can be strictly accurate.

# STUDIES OF THE MECHANISM OF CIRCULATORY INSUFFICIENCY IN RAYNAUD'S DISEASE IN ASSOCIATION WITH SCLERODACTYLIA

MYRON PRINZMETAL, M D \*

LOS ANGELES

Sclerodactylia and scleroderma are often associated with Raynaud's disease. Most frequently the changes in the skin occur after the vasospastic syndrome has been present for some time. Sclerodactylia occasionally occurs without pathologic arterial spasm and in some cases may precede the attacks of local asphyxia of the fingers. Occasionally the changes in the skin and the vasospastic attacks in the fingers begin simultaneously. Raynaud<sup>1</sup> observed the association of these closely related conditions and accurately described sclerodactylia in some of his case reports (cases 8, 11 and 15).<sup>1a</sup>

The skin and subcutaneous tissues in sclerodactylia are fibrotic, hard and inelastic. In severe forms the fibrosis may be so marked that motion of the fingers becomes impossible. The nails become deformed, the articulations are destroyed, and the bones, especially the terminal phalanges, are atrophied. The skin is stretched and pale, and the creases present in all normal skin are obliterated. The fingers become short, inert, tapering stumps, as a result of repeated attacks of gangrene.

When sclerodactylia is superimposed on Raynaud's disease, the ischemic process becomes greatly intensified, and attacks of gangrene repeatedly occur. Therapeutic measures, which have been reported to be helpful in cases of uncomplicated Raynaud's disease, are of no avail if sclerodactylia is present.<sup>2</sup>

It is my purpose in this paper to report the study of some aspects of the circulation in sclerodactylia in an effort to discover the cause of

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1 Raynaud, A. G. M. (a) *De l'asphyxie locale et de la gangrene symétrique des extrémités*, Paris, Rignoux, 1862, translation by T. Barlow. *On Local Asphyxia and Symmetrical Gangrene of the Extremities*, Selected Monographs, London, The New Sydenham Society, 1888, vol. 121, p. 1, (b) *New Researches on the Nature and Treatment of Local Asphyxia of the Extremities*, *Arch. gen. de med.* 15 and 189, 1874.

2 Boardman, W. P. *Scleroderma, with Special Reference to Its Etiology and Treatment*, *Arch. Dermat. & Syph.* 19:901 (June) 1929.

the difficult therapeutic problem and the severity of the clinical course in this condition. It is not my purpose to review the vast literature on this subject or to discuss the many unproved theories concerning the etiology of sclerodactylia, since several excellent clinical reviews have been made.<sup>3</sup>

#### REVIEW OF THE LITERATURE

The fibrotic changes are not necessarily limited to the fingers but may be generalized. If the face is involved, it may be impossible for the patient to open his mouth completely or wrinkle his forehead. Osler<sup>3a</sup> described the characteristic condition of these patients as "encased in an evershrinking, slowly contracting skin of steel."

In the rare pathologic reports made in cases of generalized scleroderma, increased fibrosis of the internal organs, such as the lungs, kidneys and bladder, has been described. Histologic examination of the skin shows hypertrophy of the collagen and the stratum granulosum. The malpighian layer is atrophied, while the corium consists of masses of white and elastic fibers.<sup>4</sup>

Adson, O'Leary and Brown<sup>5</sup> recommended sympathectomy for the relief of sclerodactylia. The results of and indications for this operation will be considered in this paper. Kerr<sup>6</sup> found that repeated exposure of the fingers to cold water may reeducate the vessels so that they do not go into spasm so readily. He found that this procedure is without value if sclerodactylia is present.<sup>7</sup>

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3 (a) O'Leary, P. A., and Nomland, R. A Clinical Study of One Hundred and Three Cases of Scleroderma, *Am J M Sc* **180** 95, 1930. (b) Boardman<sup>2</sup> (c) Lewin, G., and Heller, J. Die Sclerodermie eine monographische Studie unter Zugrundelegung von 459 aus der Literatur gesammelter und eigener Falle, *Charité-Ann* **19** 763, 1894. (d) Longcope, W. T. Hypoglycemia in Scleroderma, *J A M A* **90** 1 (Jan 7) 1928. (e) Osler, William. On Diffuse Scleroderma, with Special Reference to Diagnosis, and to the Use of Thyroid-Gland Extract, *J Cutan & Genito-Urin Dis* **16** 49 and 127, 1898. (f) Durham, R. H. Scleroderma and Calcinosis, *Arch Int Med* **42** 467 (Oct) 1928.

4 (a) Matsui, S. Ueber die Pathologie und Pathogenese von Scleroderma universalis, *Mitt a d med Fakult d k Univ zu Tokyo* **31** 55, 1924, *Presse med* **2** 142, 1924. (b) Rake, Geoffrey. Pathology and Pathogenesis of Scleroderma, *Bull Johns Hopkins Hosp* **48** 212, 1931. (c) Gordon, H. Diffuse Scleroderma, with Case Report and Autopsy Findings, *Ann Int Med* **2** 1309, 1929.

5 Adson, A. W., O'Leary, P. A., and Brown, G. E. Surgical Treatment of Vasospastic Types of Scleroderma by Resection of Sympathetic Ganglia and Trunks, *Ann Int Med* **4** 555, 1930.

6 Kerr, W. J. Raynaud's Disease. Recent Experimental Studies, *California & West Med* **34** 91, 1931.

7 Kerr, W. J. Personal communication to the author.

In addition to a more severe clinical course and a more difficult therapeutic problem, Lewis and Kerr<sup>8</sup> and Lewis and Landis,<sup>9</sup> in an exhaustive and admirable study of Raynaud's disease, found pathologic vascular reactions in the severe forms associated with sclerodactylia (cases 1, 2 and 3 of the series of Lewis and Kerr) which were not present in the mild type (cases 6, 7, 8 and 9 of the same series)<sup>10</sup>

Two main theories have been advanced as an explanation of the difference in behavior in the cases in which scleroderma was present and the cases in which it was not. In the report of Lewis and Kerr it was suggested that in the severe forms with sclerodactylia there is incomplete relaxation of the arteries between the attacks of spasm, while in mild types there is complete relaxation. Later Lewis suggested that severe forms present structural changes in the arterial walls, resulting in premature closure. A few reports have been made on structural changes in the digital arteries in Raynaud's disease<sup>11</sup> and in scleroderma.<sup>12</sup> These changes vary in frequency and intensity and may be absent in either condition. It cannot be denied, however, that when present arterial changes are an important factor in the circulatory defects of the severe forms of the disease. It is also probable that some of the pathologic vascular responses to be described are due in part to organic arterial changes.

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8 Lewis, T., and Kerr, W. J. Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation in the Fingers, a Variety of Raynaud's Disease, *Heart* **15** 7, 1929

9 Lewis, T., and Landis, E. M. Further Observations upon a Variety of Raynaud's Disease, with Special Reference to Arteriolar Defects and to Scleroderma, *Heart* **15** 329, 1931

10 Lewis and Landis<sup>9</sup> stated that such severe scleroderma developed two years after the first observation in case 1, reported in the earlier series,<sup>8</sup> that the patient could not throw her head back because of the extreme tightness of the skin. The fingers were smaller and distinctly tenser than normal. In case 2 in the same series flexion of the fingers was possible only in the fourth and fifth fingers because of the tightness of the skin, while in case 3 the condition had grown worse, so that complete flexion of the fingers was impossible, owing to changes in the skin.

11 (a) Dinkler, M. Zur Lehre von der Scleroderma, *Deutsches Arch. f. klin. Med.* **48** 514, 1891. (b) Spurling, R. G., Jelsma, F., and Rogers, J. R. Observations in Raynaud's Disease, *Surg., Gynec. & Obst.* **54** 584, 1932. (c) Grenet, H., and Isaac-Georges, P. Etude histologique des arterioles cutanees dans trois cas de syndrome de Raynaud, *Bull. et mem. Soc. med. d'hop. de Paris* **50** 151 (Jan. 29) 1926.

12 (a) Matsui<sup>4a</sup>. (b) Lewis and Landis<sup>9</sup>. (c) Dinkler<sup>11a</sup>. (d) Whitehouse, H. H. Some Observations on the Results of the Wassermann Test in Scleroderma, *J. Cutan. Dis.* **27** 535, 1909. (e) Durham, R. H. A Case of Scleroderma with Extensive Subcutaneous, Periarticular and Vascular Calcification, *Ann. Clin. Med.* **5** 679, 1926.

## PROBLEM OF INVESTIGATION

After a study of several patients with severe Raynaud's disease, one is impressed with the tight, inelastic condition of the skin found in some cases. The hypothesis seems reasonable that the tight skin of the fingers may have a constricting effect on the blood vessels and may thereby be responsible in part for the profound ischemia present in these cases. This theory has been suggested in the past<sup>13</sup> but has never been critically analyzed.

Two factors tend to make the tightness of the skin more deleterious to the circulation of the fingers than to the circulation of other areas. Owing to the circular shape of the fingers, the pressure of the skin is transmitted from all sides directly to the blood vessels. If an equal pressure is transmitted to only one side of the wall of a vessel, as may occur in parts of the body where the surface is relatively flat, only slight compression results. Moreover, the arterial blood pressure of the fingers at the level of the heart is considerably lower than the pressure in the larger and more central arteries, such as the brachial artery. Thus, it requires less external pressure to cause compression of the arteries of the fingers than compression of the larger arteries.

The theory that the tight condition of the skin and subcutaneous tissue has a constricting effect on the blood supply of the fingers in sclerodactylia has been investigated by the following observations made in cases of sclerodactylia and by artificial production of the mechanical effects of sclerodactylia on normal digits.

Investigation was made in five cases of sclerodactylia. On the basis of Lewis and Pickering's<sup>14</sup> classification of maladies grouped under the term Raynaud's disease, intermittent spasm of the digital arteries, with local nutritional changes, may be regarded as present in three instances. In these cases changes in the skin of the fingers occurred only after several years of typical intermittent spasm of the digital arteries, as indicated by the histories. The skin elsewhere was normal. In two cases mild generalized scleroderma was present. In all the cases the sclerodactylia was in a sufficiently advanced stage to cause marked limitation of motion of the fingers, and atrophy of the bone could be seen on roentgen examination. Unilateral sympathectomy was performed in three cases (table 1).

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13 Mayo, W. J., and Adson, A. W. Raynaud's Disease, Thrombo-Angitis Obliterans and Scleroderma, *Ann Surg* 96 771, 1932.

14 Lewis, T., and Pickering, G. W. Observations upon Maladies in Which the Blood Supply to Digits Ceases Intermittently or Permanently, and upon Bilateral Gangrene of Digits. Observations Relevant to So-Called "Raynaud's Disease," *Clin Sc* 1 327, 1934.

## OBSERVATIONS IN CASES OF SCLERODACTYLIA

The following observations show that the circulatory deficiency in sclerodactylia is maximal in cases in which the mechanical factor due to the tightness of the skin and subcutaneous tissue is greatest

1 The appearance of the fingers strongly suggests that the skin is hard and inelastic. It cannot be picked up or wrinkled. It is paler than the normal skin, and Brown and O'Leary<sup>15</sup> observed diminution in the number of capillaries in this condition. It is almost impossible to stretch

TABLE 1—*Clinical Data in Five Cases of Sclerodactylia*

Case, Sex, Age	Duration of Malady, Years	Fingers	Generalized Scleroderma	Necrosis	Sympathectomy	Blood Pressure, Mm	Roentgenographic Observations
1 F 52 yr	8	Moderately severe sclerodactylia, marked limitation of motion, no tapering, nails normal	None	Repeatedly observed	4 years before, Horner's syndrome	150/ 80	Absorption of tips of several terminal phalanges
2 F 27 yr	8	Marked limitation of motion, moderate tapering, deformity of nails	Moderate	Repeatedly observed	5 years before, Horner's syndrome	120/ 70	Absorption of tips of 2 terminal phalanges
3 F 50 yr	25	Marked sclerodactylia, almost complete limitation of motion, marked loss of substance of fingers	None	Observed in all fingers	Right side, Horner's syndrome	140/ 70	Complete absorption of terminal phalanges of 3 fingers
4 F 45 yr	5	Marked sclerodactylia, tapering, deformity of nails	None	Repeated ulcerations in winter	None	180/120	Slight absorption of bone of tips of several terminal phalanges
5 M 51 yr	7	Marked sclerodactylia, marked loss of substance	Moderate	Repeated ulcerations	None	140/ 70	Complete absorption of bone of several terminal phalanges

the skin of a normal finger to the same degree as one can that of a finger with sclerodactylia, but if the volar surface is pinched the skin on the dorsum becomes tight, pale and smooth and presents an appearance not unlike that of sclerodactylia

Occasionally the sclerodermatous changes do not uniformly involve all the fingers. Determinations of the cutaneous temperature verify this observation. The finger with the least disturbance of the skin is warmer than its more unfortunate fellows. A further observation is significant

<sup>15</sup> Brown, G. E., and O'Leary, P. A. Skin Capillaries in Scleroderma, *Arch Int Med* **36** 73 (July) 1925

It has been adequately shown by Lewis and Kerr that one of the most characteristic features of sclerodactylia is complete, or almost complete, inability of the fingers to maintain normal cutaneous temperature. The fingers assume and slavishly follow room temperature. It may be seen from the graph in figure 1 that the temperature of the finger with severe changes in the skin follows the room temperature as the room is cooled but that the less affected finger cools only gradually—a reaction not unlike that of the normal skin<sup>16</sup>

2 In case 3 in this series it was repeatedly noted that the tips of the fingers became dead white when the fingers were extended. On flexion the color of the skin immediately changed to that of the rest

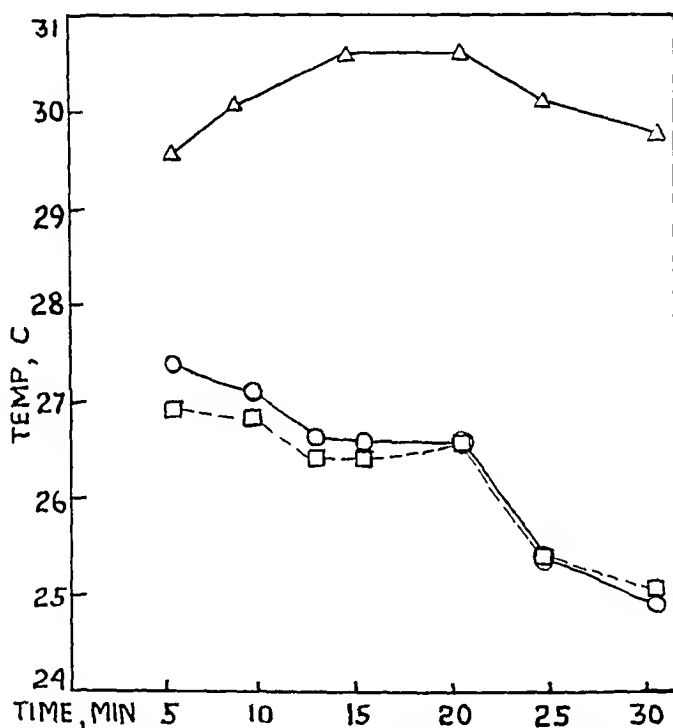


Fig 1 (case 1) —Effect of room temperature on the temperature of the skin of a digit (third on the left hand) with severe sclerodactylia and on that of a digit (first on the left hand) with slight sclerodactylia. In this chart and in the accompanying charts, except in figure 11, the curve for room temperature is indicated by a line and squares. The curve for the digit with severe sclerodactylia is indicated by a line and circles, and the curve for the digit with mild sclerodactylia, by a line and triangles. At the twentieth minute a window was opened to cool the room.

of the fingers. If while the finger was extended, gentle upward pressure was exerted on the middle phalanx, thereby relaxing the skin at the tip, the color again changed. With the use of Lewis' color scale<sup>17</sup> it was

16 Freeman, H., and Linder, F. E. Some Factors Determining the Variability of Skin Temperature, *Arch Int Med* 54:981 (Dec) 1934.

17 Lewis, T. Standard Colours for Use in the Study of Vascular Reactions of the Human Skin, *Heart* 15:1, 1929.

estimated that the intensity of the color of the skin of the finger-tip changed from tint *j* when the skin was taut to tint *c* or *d* when it was relaxed. The cutaneous temperature of this patient's finger-tips was repeatedly determined. When the fingers were extended, the temperature of the tips was always slightly below room temperature<sup>18</sup>. When the fingers were flexed, the temperature immediately rose slightly above room temperature (fig 2). The marked increase in ischemia on extension of the fingers in this case was obviously due to the tight, inflexible condition of the skin.

3 Atrophy of the terminal phalanx has been described repeatedly<sup>19</sup>. The atrophy begins at the very tip and proceeds proximally until the entire terminal phalanx is absorbed (fig 3). The atrophy never starts at the base of the terminal phalanx, as might occur if the disturbance were metabolic, nor is the process diffuse, as in the well known atrophy of disuse. The absorption of the bone corresponds to the areas of

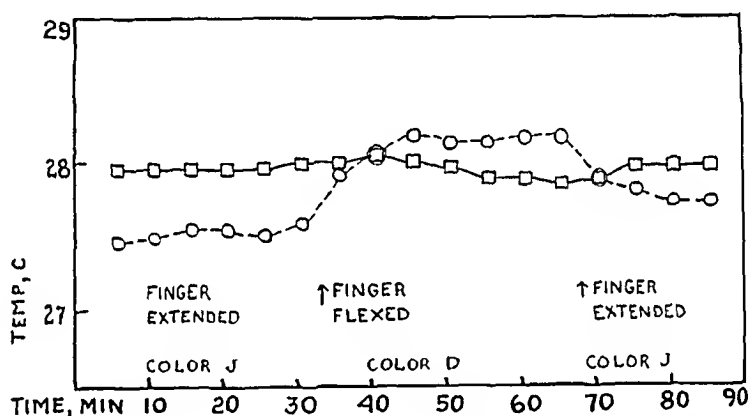


Fig 2 (case 3)—Effect of flexion and extension of the fingers on the temperature and color of the skin. After thirty-five minutes of extension the fingers were flexed. At the sixty-fifth minute they were again extended. In this chart the curve for the digit (fourth on the left hand) is indicated by a dotted line and circles.

greatest pressure of the skin, and the best explanation is that the process is similar to the atrophy which occurs in other bones subjected to persistent pressure. Christian<sup>20</sup> has expressed a somewhat similar opinion.

4 Vasodilatation as a result of sympathectomy does not improve the circulatory deficiency in sclerodactylia. As already pointed out, a characteristic feature of the very severe form is the close approximation of the temperature of the affected fingers to room temperature. In the

18 Room temperature was taken with a thermocouple from 1 to 3 cm from the skin.

19 (a) Edeiken, L. Scleroderma with Sclerodactylia, *Am J Roentgenol* **22** 42, 1929. (b) Osler<sup>3e</sup>. (c) Fox, G. H. Two Cases of Raynaud's Disease with Ocular Symptoms, *J Cutan Dis* **25** 337, 1907.

20 Christian, H., in discussion on Longcope<sup>3d</sup>.



moderately severe type the temperature of the skin may rise slightly above that of the room. It has been adequately shown that sympathectomy raises the temperature of the skin of normal subjects and of patients with mild Raynaud's disease by producing arterial dilatation. In three patients with an advanced stage of sclerodactylia no increase in the temperature of the skin could be observed, and the fingers both on the side of sympathectomy and on the side on which no operation was performed always assumed room temperature. Though the sympathetic tone of the arteries is lost, the vessels cannot open, owing to the tightness of the skin. The patients noticed no clinical improvement, and the attacks of gangrene were equally intense on the two sides. Needless to say, the patients refused to undergo operation on the opposite side.<sup>21</sup>



Fig 3 (case 3)—Roentgenogram of the hands in a case of typical sclerodactylia. The atrophy begins at the tips of the terminal phalanges (third and fifth fingers of the left hand) and progresses proximally until the entire terminal phalanx is absorbed (second finger of the left and right hand).

In view of these considerations, sympathectomy appears irrational in the treatment of this disease. Though it is assumed that there is no organic occlusion, dilatation of the vessels to any great degree is a physical impossibility because of the tight skin. More evidence will be offered on this point.

#### OBSERVATIONS ON NORMAL DIGITS

*Method of Investigation*—The mechanical effects of sclerodactylia may be produced by placing a tight rubber finger from a small surgical glove on the finger to be studied. (Size 6½ was generally used for a finger that normally required

<sup>21</sup> The operation was performed four years prior to the time of writing (1930) in the three cases.

size  $7\frac{1}{2}$  or 8) In other instances the finger was bound with small strips of zinc oxide adhesive tape This method of producing compression is probably better, since the adhesive tape is inelastic and does not expand with each systole It is difficult to evaluate the amount of compression which such constriction causes On the basis of evidence which will be given later, the pressure produced with the second method is equivalent to about 70 mm of mercury, which is considerably above the diastolic pressure in the fingers, but below the systolic pressure An effort was made to keep the pressure the same in all the experiments The glove caused a uniform compression of the finger, which was estimated to be of about the same intensity as that found in the severe forms of sclerodactylia A small opening was made in the glove over the dorsal surface of the terminal phalanx just proximal to the nail for determinations of the temperature of the skin If it was desired to determine the color of the skin, the opening was made on the ventral surface The finger may be bound for hours without causing more than a feeling of constriction As a control, a loose glove finger was placed on the corresponding digit of the other hand

*Temperature of the Skin*—As has already been pointed out, Lewis and Kerr found that a characteristic feature of the severe form of Raynaud's disease associated with sclerodactylia is the inability to maintain the normal temperature of the skin, an observation I have confirmed In the mild forms, with no cutaneous changes, the temperature of the skin is normal unless the critical cold point which produces spasm is reached

After a period of preliminary observation, the constriction already described was placed on the second finger, while a loose glove was placed as a control on the corresponding finger of the other hand The temperature of the skin of the finger with the artificial sclerodactylia gradually decreased to room temperature, while the temperature of the finger used as a control remained several degrees above room temperature If the room temperature was changed by opening or closing a window, the temperature of the skin of the bound finger closely followed the room temperature If the bound finger and the finger used as a control were placed in warm water at from 40 to 45 C for from five to ten minutes, the finger used as a control quickly assumed its former temperature on removal, while the temperature of the bound finger slowly fell to that of the room If both fingers were then placed in water at 20 C for five minutes, the temperature of the bound finger merely rose again to room temperature on removal, while the temperature of the control finger quickly attained its former value (fig 4) If the tight glove was removed, the temperature of the skin rapidly rose above the temperature of the control finger This is due to the well known phenomenon of reactive hyperemia, and the test demonstrates that complete arterial occlusion is not necessary to produce the phenomenon

*Effect of Overcooling*—If after preliminary cooling to approximately from 23 to 25 C (73.4 to 77 F) the finger is placed in ice-

water for from five to ten minutes, the blood vessels dilate considerably, and the finger subsequently becomes hotter than the control finger<sup>22</sup> This reaction was found to be normal in cases of mild Raynaud's disease, in cases in which the disease is associated with sclerodactylia, however, Lewis and Keir found that the temperature of the skin does not overshoot but merely rises to room temperature, an observation which we have confirmed<sup>23</sup>

This observation may be repeated with the experimental method The finger with the loose rubber glove, used as a control, reacts normally, while we have repeatedly observed that the temperature of the bound finger, after exposure to ice water, does not overshoot but shows a response identical to that occurring in the cases of Raynaud's disease with sclerodactylia (fig 5)

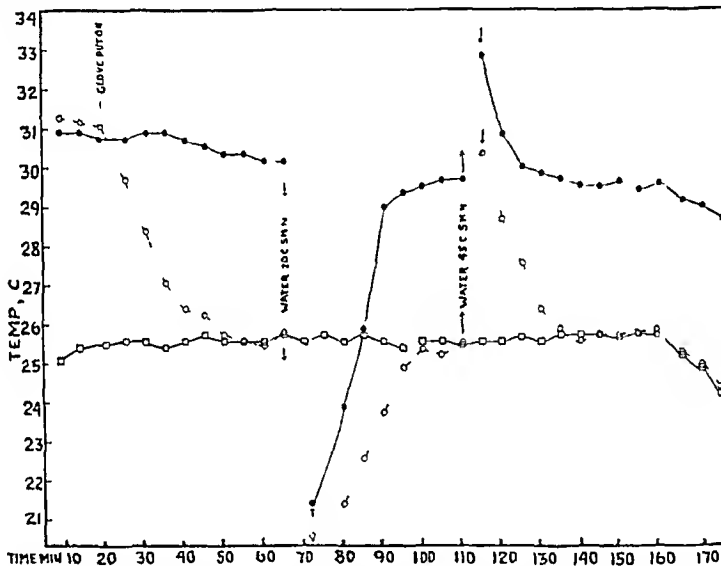


Fig 4—Effect of constriction of a normal finger on the temperature of the skin At the twentieth minute the first finger of the left hand was bound At the sixtieth minute both the bound finger and the finger used as a control were placed in water at 20 C for five minutes At the one hundred and tenth minute the fingers were placed in water at 45 C for five minutes At the one hundred and sixtieth minute the room was purposely cooled by opening a window In this chart and in the charts in figures 5, 6 and 8 the curve for the finger in which artificial scleroderma was produced (first digit of the left hand in this experiment) is indicated by a dotted line and circles, and the curve for the finger used as a control (first digit of the right hand in this experiment), by a solid line and solid circles

22 Lewis, T Observations upon the Reactions of the Vessels of the Human Skin to Cold, *Heart* **15** 177, 1930, Supplementary Notes upon the Reactions of the Vessels of the Human Skin to Cold, *ibid* **15** 351, 1931, *The Blood Vessels of the Human Skin and Their Response*, London, Shaw & Sons, 1927

23 Clifford Wilson and I have found that this reaction may be absent in some patients with peripheral vascular disease

*Volume of the Digital Pulse*—The volume of the digital pulse at different temperatures may be determined by means of a small finger plethysmograph. The oscillations are transmitted to a Frank capsule, magnified by an optical system and recorded on a moving photographic film. With this method changes in volume of 0.001 cc may be determined. Tracings are taken at 20, 25, 30, 35, 40 and 45 C, respectively, after the finger has been exposed to each temperature for ten minutes. At the higher temperatures the magnitude of the oscillations is normally greatly increased because of arterial dilatation and increase in blood flow. Lewis and Keir found that in cases of uncomplicated Raynaud's disease the curve is normal but that in cases in which the disease is associated with sclerodactylia the oscillations are greatly reduced at the higher temperatures.

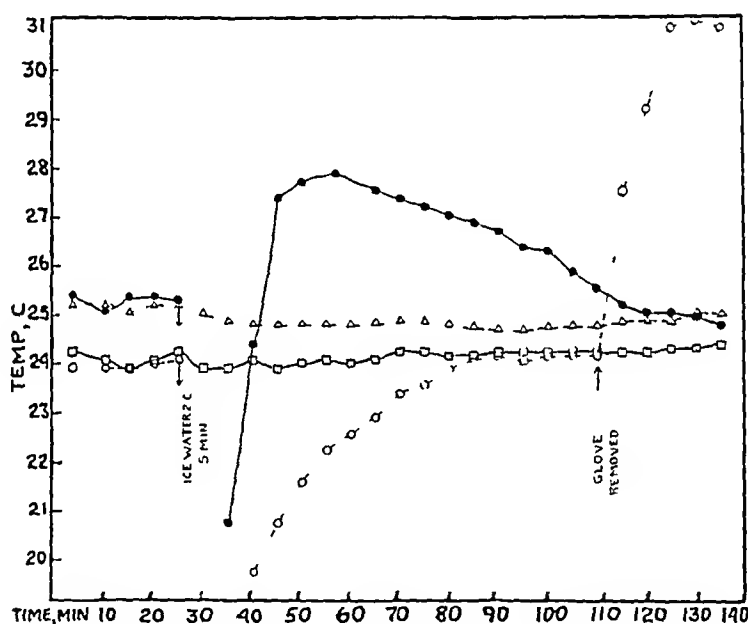


Fig 5—Effect of overcooling on the temperature of the skin. At the twenty-fifth minute both the bound finger (second digit of the left hand) and the finger used as a control (second digit of the right hand) were placed in ice-water for five minutes. On the one hundred and tenth minute the constriction was removed. The curve for a finger with mild sclerodactylia (fourth finger on the right hand) is indicated by a line and triangles.

This experiment was repeated many times with a finger in which artificial sclerodactylia was produced. The resulting curve is similar in all respects to the curves obtained by Lewis (fig 6).

If the pressure on the finger is slight, the magnitude of the oscillations is greatly increased. This is probably due to better mechanical transmission of the pulse beat and is analogous to the increase in the magnitude of the pulsations obtained by a Pachon oscillometer when the pressure is considerably below the systolic.

The effect of pressure on the oscillations in the pulse volume was studied in the following manner

The finger was placed in a glass tube closed at one end and connected by a side arm with a mercury manometer and an air-pump, so that any desired pressure could be obtained. Circular rubber tubing from a glove finger lightly grasped the

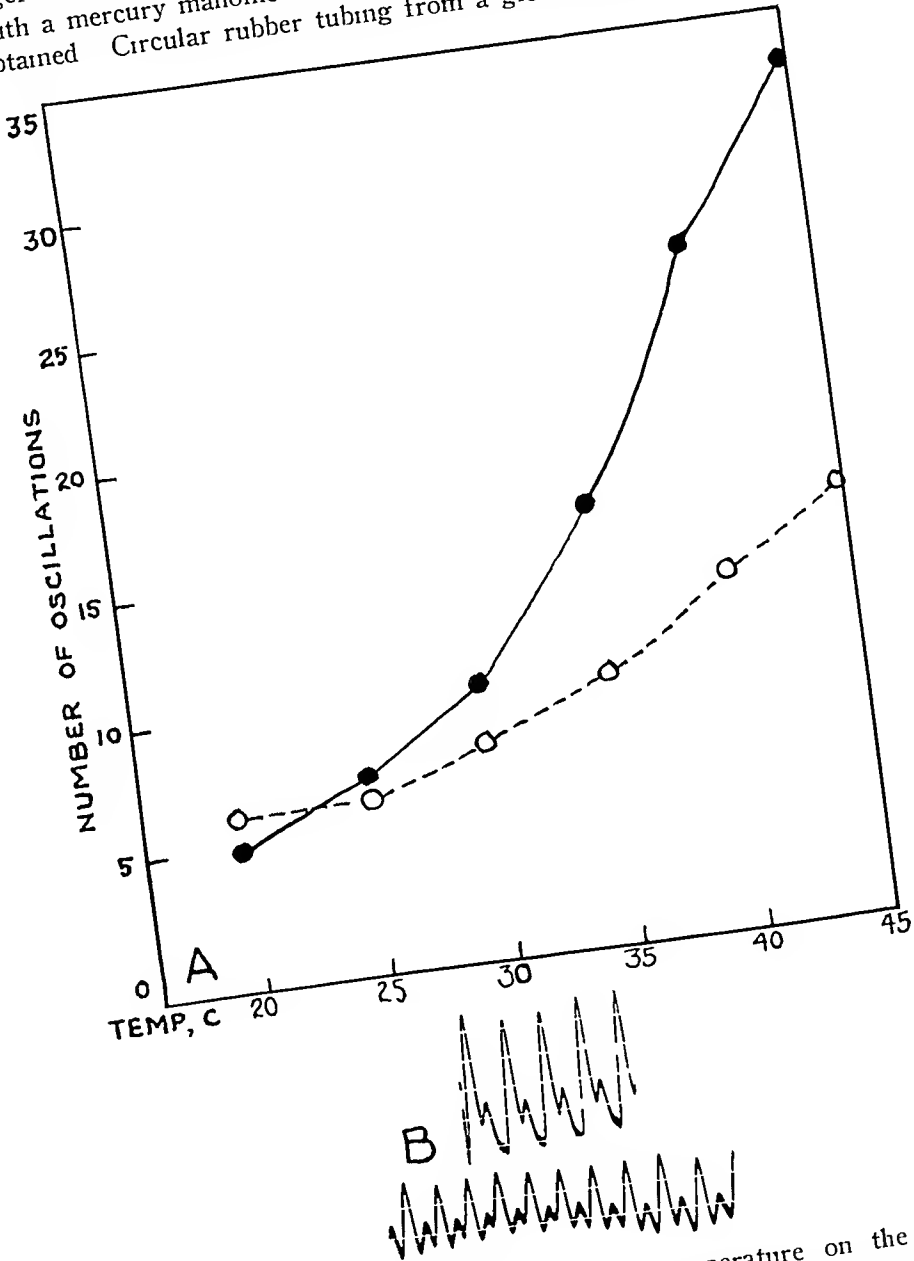


Fig 6—(A) Graph showing the effect of temperature on the plethysmographic oscillations of the pulse of a constricted finger and on those of the same finger with no constriction. The increment is 0.001 cc. (B) Tracings taken at 40 C of the plethysmographic oscillations of the pulse of a normal finger (the upper tracing) and of the same digit while constricted (lower tracing)

proximal end of the finger and the glass tube so that when the pressure was raised the opening was sealed and a uniform pressure was exerted on the entire finger. The tube was filled with water at a known temperature. The level of

the water was read in the narrow side arm and the pulsations were observed. The pressure in the tube could be changed at will, and the effect of various pressures on the pulsations observed (fig 7)

At a pressure of from 20 to 50 mm of mercury the oscillations were greatly increased over the normal, the greatest being obtained at from 30 to 50 mm of mercury. At a pressure above 60 mm of mercury the oscillations became smaller than normal, until they completely disappeared at from 90 to 100 mm of mercury, the systolic pressure of the fingers at the level of the heart. From this observation it is obvious that the pressure exerted on the finger in these experiments is from 60 to 90 mm of mercury. It is not lower, for the oscillations were smaller than normal. It is below 90 mm of mercury, or systolic pressure, for pulsations were present.

*Sympathetic Vasodilatation*—It has been shown by Lewis<sup>24</sup> that if the body is heated after preliminary cooling sympathetic vasodilatation

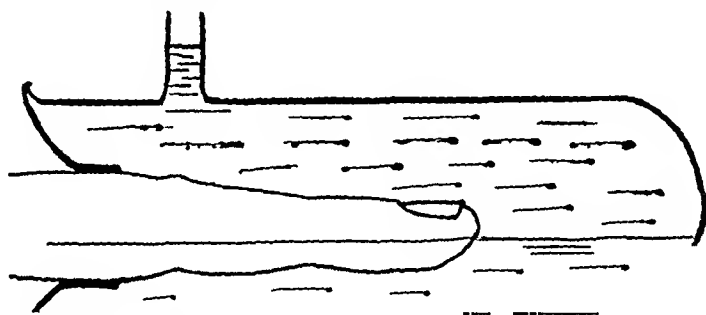


Fig 7—Diagram of the glass tube. The side arm is connected with a mercury manometer and a hand air-pump.

of the arterioles of the extremities takes place and that this reaction may be used as a test for occlusive arterial disease. Landis and Gibbon<sup>25</sup> modified this procedure by placing one or two extremities in hot water and measuring the temperature of the skin of the limb to be tested. If the cutaneous temperature of this limb does not rise appreciably, it is assumed that an organic arterial lesion is present. In cases of sclerodactylia we have found that no rise in temperature takes place. In the following experiment it was shown that tight skin, such as occurs in sclerodactylia, may produce the same type of reaction as organic arterial occlusion.

A tight binding was placed on a finger and a loose binding on a finger to be used as a control, after preliminary cooling. Both feet

24 (a) Lewis, T. Experiments Relating to Peripheral Mechanism Involved in Spasmodic Arrest of Circulation in the Fingers. A Variety of Raynaud's Disease, *Heart* **15** 7, 1929. (b) Lewis, T, and Pickering, G. W. Vasodilatation of the Limbs in Response to Warming the Body, *Heart* **16** 33, 1933.

25 Landis, E. M., and Gibbon, J. H., Jr. Simple Method of Producing Vasodilatation in Lower Extremities, with Reference to Its Usefulness in Studies of Peripheral Vascular Disease, *Arch Int Med* **52** 785 (Nov.) 1933.

were then placed in water at from 43 to 45 C. The control finger reacted normally and soon reached a temperature of 32 C (89.6 F). The temperature of the bound finger, which had previously been that of the room, rose only 1.5 C (2.7 F). Another characteristic may be noted. While the control finger began to react from ten to fifteen minutes after the feet were placed in hot water, the bound finger did not react until ten minutes later, an observation which Landis made in cases of organic occlusion (fig. 8). If the constriction was slightly more intense, no increase in the temperature of the finger took place.

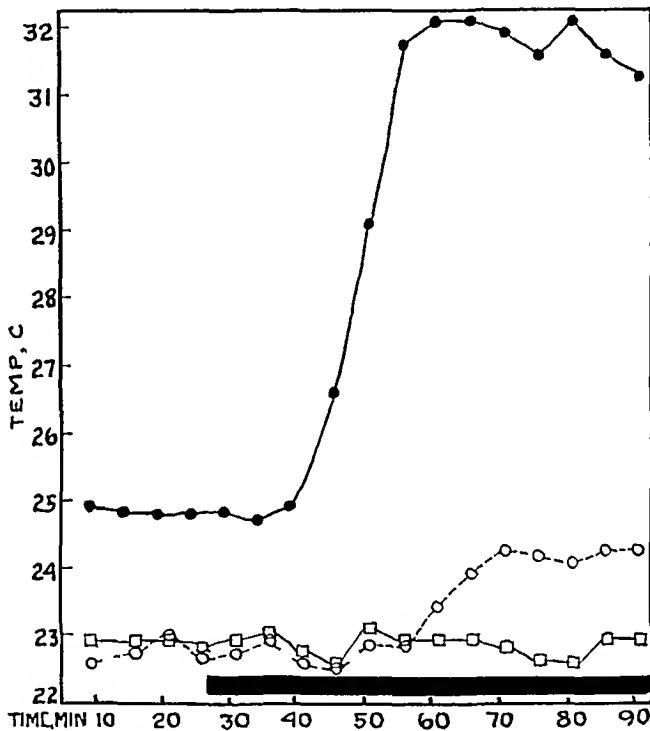


Fig. 8—Effect of the Landis test on the temperature of the skin of the finger used as a control (second on the right hand) and of the bound finger (second on the left hand). At the twenty-sixth minute, as indicated by the solid rectangle, the left foot was placed in warm water at a temperature of from 43 to 45 C.

These observations support my explanation of the lack of therapeutic response to sympathectomy in cases of sclerodactylia, and they further show the irrationality of the procedure in the treatment of this condition.

*Effect of Histamine*—We have observed that if from 0.1 to 0.2 cc of a mixture of a 1:1,000 dilution of histamine hydrochloride and a small amount of procaine hydrochloride is slowly injected into the terminal phalanx of a finger or toe after preliminary cooling the temperature of the skin around the site of injection rapidly rises to the maximum. If an organic arterial lesion is present, the increase is greatly

reduced or is absent. We have used this test in several cases of peripheral vascular disease in order to determine the degree of spasm. In all cases in which tests have so far been made, we have found complete correlation between the results of this test and those of the Landis test (fig 9). The main advantage of this test is its simplicity and the rapidity with which it can be performed.

If this test is performed on patients with an advanced stage of sclerodactylia, no rise in temperature takes place (table 2).<sup>26</sup> In cases of uncomplicated Raynaud's disease there is a normal rise in temperature. If a normal finger is bound in the manner already described, there is little or no increase in temperature, while the normal reaction takes place in the finger used as a control.

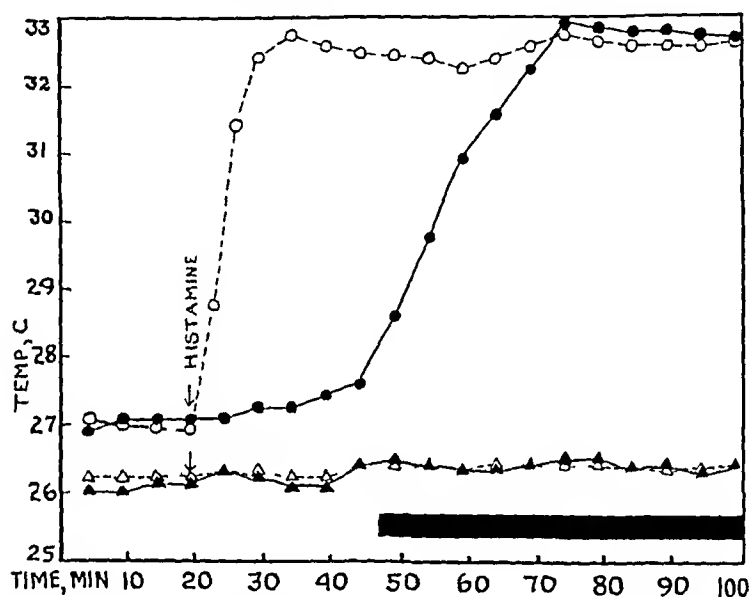


Fig 9—Effect of the injection of 0.2 cc of histamine on the temperature of the skin of the extremities of a patient with thrombo-angitis of the lower extremities. The injections were made in the first toe of the right foot and the fourth finger of the right hand. The lack of response of the temperature of the toes and the rapid increase in the temperature of the fingers are shown. At the forty-sixth minute, as indicated by the black rectangle, the left arm was placed in warm water at a temperature of from 43 to 45 C as a control test, with identical results. The room temperature varied from 23 to 25 C. In this chart the curve for the first toe of the right foot is indicated by a line and hollow triangles, the curve for the second toe of the same foot, by a line and solid triangles, the curve for the third finger of the right hand, by a line and solid circles, and the curve for the fourth finger of the right hand, by a line and hollow circles.

<sup>26</sup> We have recently observed an increase in temperature of 1.5 C (2.7 F) after the injection of histamine in a patient with sclerodactylia, who was not included in this series. There had been no rise in temperature following the heat test performed by the Landis technic. After an injection of histamine into a finger, it was impossible to induce an attack of arterial spasm in that finger by exposure to cold water.



*Effect on Blood Flow of Alteration in Atmospheric Pressure*—There has been a recent revival of altering the atmospheric pressure as a therapeutic procedure to increase the blood flow to the extremities<sup>27</sup> in disease of the peripheral arteries. It has been shown that the blood flow, as measured by the temperature of the skin, may be greatly increased by this procedure and that spectacular benefit often results. In Raynaud's disease a somewhat similar method has been tried, apparently with great success,<sup>28</sup> but, unfortunately, not under controlled experimental conditions. We have made the following observations in regard to this therapeutic procedure.

A binding was placed on the finger sufficiently tight to cause enough compression to eliminate any rise in the temperature of that finger during the Landis

TABLE 2—*Temperatures of the Skin of the Fourth Fingers of the Left and Right Hands in Case 4 During the Landis Test and After Injection of Histamine\**

Time	Room Temperature, C	Temperature of Left Finger, C	Temperature of Right Finger, C
10 15	29.2	30.7	28.7
10 20	27.5	30.4	28.6
10 25	24.5	26.8	26.3
10 30	22.7	24.4	24.2
10 35	20.2	20.5	20.3
10 40	20.1	20.3	20.2
10 50	20.4	20.4	20.2
10 55	20.5	20.5	20.6
11 00	20.7	20.9	20.9
11 05	21.4	20.7	20.7
11 10†			
11 15	20.0	19.5	19.5
11 20	19.3	19.1	18.8
11 30	19.2	18.7	18.7
11 40	19.3	18.7	18.5
11 50	20.2	19.7	19.4
12 00	20.5	19.7	19.5
12 10	20.6	19.6	19.7
12 20	20.9	19.9	19.8†
12 30	21.2	20.1	20.0
12 40	21.3	20.1	20.0

\* No dilatation of the arteries followed either test.

† Both feet in water, 45 C.

‡ Injection of 0.2 cc. of a 1:1,000 dilution of histamine hydrochloride and procaine hydrochloride into the right finger.

test or after the injection of histamine. Thus, sympathetic vasodilator impulses could not increase the blood flow. The digit was then placed in a small glass plethysmograph, which was connected to a vacuum pump. A pressure of —100 mm. of mercury was maintained for fifteen seconds, alternating with a pressure of 0 or of +10 mm., held for a shorter period.

27 (a) Landis, E. M., and Gibbon, J. H. Effects of Alternate Suction and Pressure in Circulation in the Lower Extremities, *Proc Soc Exper Biol & Med* **30** 593, 1933. (b) Reid, M. R., and Herrmann, L. G. Treatment of Obliterative Vascular Disease by Means of Intermittent Negative Pressure Environment, *J Med* **14** 200, 1933. (c) Herrmann, L. G., and Reid, M. R. The Pavaex Treatment of Obliterative Arterial Disease of the Extremities, *ibid* **14** 524, 1933. (d) Herrmann, L. G. Syphilitic Peripheral Vascular Diseases, *Am J Syph & Neurol* **17** 305, 1933.

28 Braeucker, W. Die Behandlung der Raynaudschen Krankheit, *Arch f klin Chir* **167** 807, 1931.

It was found that a slight rise in the temperature of the skin of about  $1.5^{\circ}\text{C}$  ( $2.7^{\circ}\text{F}$ ) often took place and that improvement in the color of the skin occurred (fig 10). This increase in circulation, although slight, is of significance, since sympathetic vasodilator impulses induced by the Landis test were insufficient to open the compressed arterioles but the suction apparently partially relaxed the artificial compression, allowing more blood to flow into the finger.

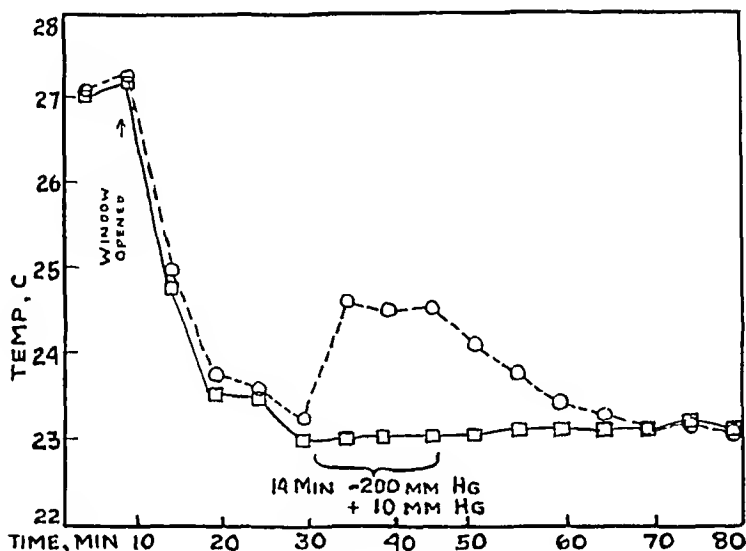


Fig 10—Effect of alteration of the atmospheric pressure on the temperature of the skin of a constricted finger. No rise in temperature took place during the Landis test or after injection of histamine which had been made prior to the constriction. In this chart the curve for the constricted finger is indicated by a line and hollow circles.

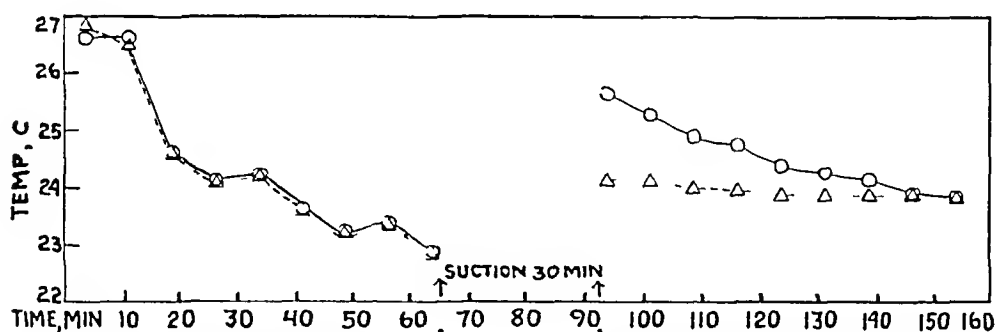


Fig 11—Effect of altering the atmospheric pressure in case 3. No increase in the temperature of the skin followed sympathectomy, which had previously been performed. In this chart the curve for room temperature is indicated by a dotted line and triangles, and the curve for the constricted finger (fourth on the left hand) by a solid line and circles.

We have had the opportunity of studying this procedure in a patient with sclerodactylia after complete unilateral sympathectomy, a procedure which, as already shown, had not the slightest effect on the

temperature of the skin (case 3) That the sympathetic nerves were cut was proved by the inability of the patient to perspire on the side of operation and by the presence of the Horner syndrome Suction caused a definite improvement in the color of the skin, especially in the intensity, and there was a slight but definite rise in the temperature of the skin above that of the room (fig 11) This is the only procedure we were able to discover which increased the blood supply of the fingers of this patient Tingling of the fingers frequently occurs during the treatment Lewis and his associates<sup>29</sup> showed that this is due to recovery of the nerves from loss of blood supply

When an attack of arterial spasm was produced in the fingers by prolonged exposure to water at 15 C, we were unable to relieve the spasm by this procedure in two instances In one patient the area of cyanosis increased during the suction On the basis of these observations, it is not likely that this procedure has any therapeutic benefit in cases of uncomplicated Raynaud's disease

#### COMMENT

From the review of the literature it is apparent that Raynaud's syndrome may be divided into two fairly distinct types, which differ clinically, therapeutically and experimentally In the form associated with sclerodactylia the clinical picture is more severe, the therapeutic problem is more difficult, and the experimental vascular reactions differ from those in the uncomplicated form In spite of these differences, there is a fundamental similarity in that there are attacks of cyanosis and blanching on exposure to cold in both types

We believe that we have demonstrated that the mechanical effects of tight skin are sufficient to explain the severe clinical course, the difficult therapeutic problem and the pathologic vascular response found in sclerodactylia In addition, morphologic studies have shown that arterial lesions, which undoubtedly aggravate the condition, may be present The relative importance of each factor cannot be ascertained at present If cases of Raynaud's disease are found in which normal skin but abnormal vascular responses occur, one may be sure that arterial changes are present If the vascular reactions are normal, no marked arterial lesions or changes in the skin are present

It seems reasonable to assume that the ischemia produced by a tight skin is more severe than that induced by organic arterial lesions, since, in addition to a decrease in the blood flow, there is compression of the capillaries, which diminishes the nutrition of the tissues

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<sup>29</sup> Lewis, T, Pickering, G W, and Rothschild, P Centripetal Paralysis Arising Out of Arrested Blood Flow to the Limb, Including Note on a Form of Tingling, *Heart* **16** 1, 1933

In all the roentgenograms taken in the cases in our series, the interphalangeal joints appeared normal. It is therefore probable that the marked limitation of motion of the fingers is due to the fibrosis which splints the finger rather than to arthropathy.

In view of these observations, the rational therapeutic approach to Raynaud's disease in association with sclerodactylia may be considered. As indicated early in this paper, sympathectomy offers no hope for relief. Reeducation by exposure to cold and the use of vasodilator drugs, procedures which are recommended in cases of Raynaud's disease in which no complications occur, are also ineffective. Until an agent is found which reduces fibrous tissue and remedies organic changes in the arteries, treatment at best is unsatisfactory and can be only symptomatic. It occurred to us that if the skin could be split longitudinally on the lateral and medial surfaces of the fingers, the edges of the tight skin might retract and thereby allow the vessels to expand. We hoped to fill the defect by means of a skin graft. In one patient (case 5),<sup>30</sup> on whom Dr. J. Homer Woolsey operated in this manner, no retraction of the skin took place. The scar tissue in this case at least extended all the way to the bone, and improvement did not occur. If conditions can be found in which the fibrosis involves only the skin, this procedure may be beneficial.

The most rational procedure seems to be the alternating use of suction and compression, as recommended by Herrmann and Landis. We have shown not only experimentally but clinically that this procedure may increase the blood flow to the fingers when other procedures, including sympathetic vasodilatation, fail. The mechanism of improvement in these cases is probably the stretching of the skin, which permits better blood flow. We are unprepared to state whether this procedure will prove beneficial in all cases, nor are we sure how great the degree of benefit will be.

#### CONCLUSIONS

1 Raynaud's syndrome in association with sclerodactylia has a more severe clinical course and presents a more difficult therapeutic problem than uncomplicated Raynaud's disease, and the experimental vascular reactions differ in the two conditions.

2 Important causal factors in sclerodactylia are the tight, inelastic skin and subcutaneous tissue of the fingers, which constrict the blood vessels and diminish the blood flow.

3 In sclerodactylia the areas of greatest circulatory insufficiency coincide with the areas of greatest change in the skin. Determinations of the temperature of the skin verify this contention.

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<sup>30</sup> This patient was in the medical service of Dr. William J. Kerr of the University of California Hospital.

4 Evidence is presented which indicates that the atrophy of the terminal phalanx in sclerodactylia is probably due to pressure of the tight skin

5 Whereas sympathectomy raises the temperature of the normal skin and the temperature of the skin of patients with uncomplicated Raynaud's syndrome, little or no rise in temperature takes place if severe sclerodactylia is present, and no clinical improvement follows. An important factor in this result is the tight skin which constricts the vessels and does not permit dilatation of the arteries after vasomotor tone is abolished

6 It was demonstrated in one case that if the tight skin of the finger tip is relaxed, slight but definite improvement in circulation, as determined by the color and temperature of the skin, takes place

7 If a binding of about the same degree of tightness as that present in sclerodactylia is placed on a normal finger, the abnormal vascular reactions found in sclerodactylia may be duplicated. It has been shown by this method that the temperature of the skin assumes and follows room temperature, the characteristic vasodilator phenomenon on exposure to cold is not shown and smaller plethysmographic oscillations occur at high temperatures

8 Vasodilator impulses induced by the Landis heat test for arterial occlusion cause little or no increase in the temperature of the skin in sclerodactylia. Similarly, if a normal finger is bound, little or no rise in temperature takes place

9 A simple test for arterial occlusion may be performed by the injection of histamine into the terminal phalanx of the finger or toe to be tested. If no organic occlusion is present, the temperature of the skin rises in a short time

10 In cases of severe sclerodactylia no rise in temperature takes place after the injection of histamine. If the normal finger is bound, similar results are obtained

11 The use of intermittent suction, recommended by Herimann and Landis, may cause an increase in circulation in cases of sclerodactylia, as determined by the temperature and color of the skin, though sympathectomy has failed to produce improvement. It is suggested that the mechanism of improvement is the relaxation of the tight skin. This seems to be the only method available at present which may prove beneficial. This procedure is probably ineffective in the relief of attacks of uncomplicated Raynaud's disease

Dr George E. Wever, San Francisco, and Dr Florence Haynes, Boston, gave help in various experiments. Dr James C. White of the Massachusetts General Hospital gave permission for the study of three of his cases

# Progress in Internal Medicine

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## INFECTIOUS DISEASES

### REVIEW OF THE CURRENT LITERATURE

HOBART A. REIMANN, M.D.

PHILADELPHIA

The labor of reviewing the literature on infectious diseases has been considerably lightened by the recent publication of a number of comprehensive surveys covering various aspects of the subject<sup>1</sup>. Notable among these are reviews concerning gonococcic infections, arthritis, bacteriophage, lymphogranuloma venereum (lymphogranuloma inguinale), influenza, undulant fever and Weil's disease. Advances in the knowledge of syphilis and microbic dissociation will be discussed in forthcoming papers<sup>2</sup>. The portions of the subjects dealt with in these papers will therefore not be discussed in the present review.

### PNEUMONIA

According to various statistics, pneumonia occupies second or third place in tables of mortality rates and is responsible for about 100,000 deaths a year in the United States. Hence, any advances in its prevention or treatment are of great significance. The seriousness of the problem led to an intensive study over a four year period in Massachusetts, and recently campaigns against this disease have been inaugurated in the states of New York, Connecticut and Maine and in Detroit. Because of the favorable results obtained by physicians in general prac-

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From the Department of Medicine, Jefferson Medical College

1 Thomas, R. B., and Bayne-Jones, S. Report of the Committee for Survey of Research on the Gonococcus and Gonococcus Infection, *Am J Syph, Gonorr & Ven Dis (supp)* **20** 1-179 (Jan) 1936. Hench, P. S., Bauer, W., Fletcher, A. A., Ghrist, D., Hall, F., and White, T. P. Present Status of the Problem of "Rheumatism" and Arthritis, *Ann Int Med* **9** 883-982 (Jan) 1936. Krueger, A. P. The Nature of Bacteriophage and Its Mode of Action, *Physiol Rev* **16** 129-172 (Jan) 1936. Wassen, E. Studies of Lymphogranuloma Inguinale from Etiological and Immunological Points of View, *Acta path et microbiol Scandinau (supp)* **23** 1-168, 1935. Klotz, O., and Holman, W. L. Studies on Influenza, *Am J M Sc* **191** 426-446 (March) 1936. Carpenter, C. M., and Boak, R. A. The Treatment of Human Brucellosis. A Review of Current Methods, *Medicine* **15** 103-127 (Feb) 1936. Jeghers, H. J., Houghton, J. D., and Foley, J. A. Weil's Disease, *Arch Path* **20** 447-476 (Sept) 1935.

2 Moore, J. E. Syphilis. A Review of the Recent Literature, *Arch Int Med*, to be published. Hadley, P. *Physiol Rev*, to be published.

tice with the typing of pneumococci and specific serum therapy, Massachusetts has undertaken to supply antiserum for typing and therapeusis free of charge. The results of the study have been summarized in a handbook<sup>3</sup>

The practice of regarding pneumonia from an etiologic point of view is constantly gaining ground. It is well established that the term pneumonia includes a group of acute infections of the lungs, each caused by specific organisms. The clinical characteristics of the forms of pneumonia due to pneumococci of types I, II, III and VIII which permit each to be regarded as an entity have already been described. During the year further reports have appeared. Smith<sup>4</sup> studied a small epidemic of staphylococcic pneumonia among infants in a Glasgow hospital. Bullowa<sup>5</sup> analyzed the results of his large experience with typing pneumococci and found that the organisms recovered from the sputum of patients with pneumonia were of the type responsible for the disease in over 93 per cent of cases, thus revealing the reliability of the methods in current use. The simple and rapid Neufeld capsule-swelling test, a test which can be used in office practice, was found to be reliable in 76 per cent of cases. Numerous investigators are depending more on puncture of the lung to obtain material for typing<sup>6</sup>. The difficulty of obtaining sputum from infants has been largely overcome by aspirating the swallowed sputum from the stomach by means of a small rubber tube<sup>7</sup>. Belk's<sup>8</sup> statistical study of the value of concentrated serum therapy shows a reduction of mortality due to type I infection from 25 per cent in cases in which the serum was not given to 15 per cent in the cases in which the serum was used, in type II infections the rate was reduced from 37 to 30 per cent. These figures are more impressive when the cases of bacteremia are analyzed separately. Large doses of antiserum are necessary in treating type II pneumonia<sup>8</sup>. In another study<sup>3</sup> serum treatment reduced the death rate in cases of type I infection from 25

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3 Lord, F. T., and Heffron, R. *Lobar Pneumonia and Serum Therapy*, New York, Commonwealth Fund, 1936.

4 Smith, C. M. *Staphylococcal Pneumonia Among Infants in a Maternity Hospital*, *Lancet* **1** 1204-1207 (May 25) 1935.

5 Bullowa, J. G. M. *The Reliability of Sputum Typing and Its Relation to Serum Therapy*, *J. A. M. A.* **105** 1512-1518 (Nov. 9) 1935.

6 Sappington, S. W., and Favorite, G. O. *Lung Puncture in Lobar Pneumonia*, *Am. J. M. Sc.* **191** 225-234 (Feb.) 1936.

7 Wittes, S. A., and Bullowa, J. G. M. *Gastric Aspiration in Children with Pneumonia to Obtain Material for Pneumococcus Typing*, *Am. J. Dis. Child.* **50** 1404-1408 (Dec.) 1935.

8 Belk, W. P. *The Specific Treatment of Lobar Pneumonia*, *J. A. M. A.* **105** 868-871 (Sept. 14) 1935. Finland, M., and Dowling, H. F. *The Dose of Antibody Effective in the Treatment of Pneumococcus Type II Pneumonia*, *Am. J. M. Sc.* **191** 658-673 (May) 1936.

to 11 per cent and in those of type II infection from 41 to 27 per cent. Thus far the greatest benefits have accrued from type I and type VII antiserum. Antiserum for infections of types IV, V, VI, VIII and XIV will soon be commercially available. Type VII infections accounted for about 6 per cent of the cases of pneumonia in Bullowa's<sup>9</sup> series, with an average mortality rate in cases of bacteremia in which serum was not administered of nearly 70 per cent, as compared with 25 per cent in cases in which serum was administered. Pneumonia due to the type VIII pneumococcus was usually less severe than that due to certain other types, especially type III, with which type VIII is closely related immunologically.<sup>9</sup> Goebel<sup>10</sup> has shown that the basis for this relationship may rest in the identity of the aldobionic acid nucleus common to the carbohydrate of these two types. Type VIII organisms invade the blood stream more frequently than those of type III, but fortunately with a much lower mortality. Type VIII pneumococci are prone to invade the meninges after subsidence of the pneumonia. The results of therapy with type VIII antiserum were striking. In 21 cases in which the serum was not used the mortality was 62 per cent, in the 12 cases in which it was used, 16 per cent. Cecil<sup>11</sup> recently analyzed 500 cases of type III pneumonia.

Pneumonia caused by *Pneumococcus* type XIV is especially common in young children, often being of the lobar form in infants, with prolonged illness.<sup>12</sup> In adults this type often causes severe illness, and the organism invades the blood, pleura, pericardium and meninges more frequently than many other types of pneumococci. Specific serum therapy appears to shorten the course of the illness.

An excellent small monograph describing the methods of typing and specific treatment of pneumonia has recently been published.<sup>3</sup>

*Heterophile Antibodies*—Much unwarranted commercial publicity has been given to the use of antipneumococcus serum containing heterophile antibodies. On the basis of certain academic investigations this serum has been made available prematurely to the general practitioner without adequate clinical trial. While it is necessary and desirable to

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9 Bullowa, J. G. M. Pneumonias Due to *Pneumococcus* Type VIII, *Am J M Sc* **190** 65-83 (July) 1935.

10 Goebel, W. F. Chemo-Immunological Studies on Soluble Specific Substance of *Pneumococcus*. II. Chemical Basis for the Immunological Relationship Between the Capsular Polysaccharides of Types III and VIII *Pneumococcus*, *J Biol Chem* **110** 391-398 (July) 1935.

11 Cecil, R. L., Plummer, N., and McCall, M. *Pneumococcus* Type III Pneumonia. An Analysis of Five Hundred Cases, *Am J M Sc* **191** 305-319 (March) 1936.

12 Bullowa, J. G. M. Pneumonia Due to *Pneumococcus* Type XIV (Cooper) and Its Treatment with Specific Antiserum, *J Clin Investigation* **14** 373-383 (July) 1935.



test all claims as to the effectiveness of any new therapeutic agent under controlled conditions, it seems especially deplorable to place on the market an untried remedy for a disease as serious as pneumonia. What is worse is the tendency to regard the serum in question as a panacea for all types of pneumococcic pneumonia and to discredit the necessity of typing the pneumococci, a fact which has been laboriously established after twenty-five years of work. Finland and his associates<sup>13</sup> failed to discover any indication that a heterophile antibody has any significance in cases of lobar pneumonia in human beings. They found no constant relationship between the hemolytic titer of the serum and the outcome of the disease. They state "The claims that are alleged to indicate the superiority of antipneumococcus serum containing heterophile antibody over the unadulterated type-specific antibody may temporarily increase the sale of this material to an ever hopeful and credulous medical public."

*Artificial Pneumothorax*—Numerous reports of the favorable effects of induced pneumothorax in the treatment of pneumonia in small groups of patients have appeared during the year. Blake and his associates<sup>14</sup> recommend large initial doses (1,800 cc) given at the rate of 10 or 15 cc per minute, followed by refills of smaller amounts, when necessary, at intervals of four or eight hours. Their studies show that when established early in suitable cases, pneumothorax appears to be a useful therapeutic procedure. Their work is summarized in an extensive review.<sup>14b</sup> They believe that the beneficial effect obtained is accounted for by the "lung rest theory," and they suggest that collapse therapy is effective because lobar pneumonia most frequently commences at the hilus and spreads outward. This theory is open to serious question since both Ude<sup>15</sup> and Rigler,<sup>16</sup> whose papers are not mentioned in the review, emphasize the great frequency with which lobar pneumonia commences peripherally. Furthermore, several of the roentgenograms reproduced in Blake's<sup>14b</sup> paper (figs 6 and 7) show consolidation commencing in the periphery of the lung. Other observers do not regard

13 Finland, M., Rueggsegger, J. M., and Felton, L. D. Heterophile Antibodies in Pneumonia, *J. Clin. Investigation* **14** 683-690 (Sept.) 1935, Should Heterophile Antibody Be Used in Treatment of Pneumococcic Pneumonia? *J. A. M. A.* **105** 1180-1182 (Oct. 12) 1935.

14 Blake, F. G., Howard, M. E., and Hull, W. S. (a) Artificial Pneumothorax in the Treatment of Lobar Pneumonia, *J. A. M. A.* **105** 1489-1495 (Nov. 9) 1935, (b) Artificial Pneumothorax in Lobar Pneumonia, *Medicine* **15** 1-102 (Feb.) 1936.

15 Ude, W. H. Roentgenologic Studies in Early Lobar Pneumonia, *Am. J. Roentgenol.* **26** 691-695 (Nov.) 1931.

16 Rigler, L. X-Ray Diagnosis of Lobar Pneumonia, in Piersol, G. M., Bortz, E. L., and others. *The Cyclopedia of Medicine*, Philadelphia, F. A. Davis Company, 1934, vol. 9, pp. 1072-1077.

this mode of therapy with optimism Bullowa and Mayer<sup>17</sup> believe that general practitioners will not be justified in employing it until many more carefully controlled studies are made They regard pneumothorax as a hazardous and unnecessary procedure in cases of the types of lobar pneumonia for which specific antisera exist Abernethy and his associates<sup>18</sup> at the Hospital of the Rockefeller Institute studied 6 apparently ideal and carefully controlled cases in which pneumothorax was induced They concluded that large amounts of air may be introduced without any harm and that pleural pain is often relieved by small amounts but that large amounts frequently cause increased dyspnea, tachypnea, cyanosis and substernal pain, with which statement Bullowa and I concur Massive amounts given early in the course of the disease according to Blake's technic did not influence the course favorably in 6 cases, there was no reduction of toxicity or apparent shortening of the disease In 1 patient the pneumonia spread to the other side

*Prophylaxis*—Lister and his associates<sup>19</sup> have published the results of a twenty-four year study of the prophylaxis of pneumonia in native miners in South Africa They again point out that pneumonia is composed of a group of specific disease entities Before 1926 pneumonia was caused chiefly by pneumococci, but since that time pneumonia caused by streptococci, staphylococci and *Bacillus influenzae* has become more prevalent It seems that prior to 1926 the use of pneumococcus vaccine distinctly lowered the incidence of the disease until the appearance of other organisms as etiologic agents The increase of the morbidity and mortality rate caused by these organisms led to the addition of streptococci, staphylococci and influenza bacilli to the vaccine These antigens were used not so much to prevent infection of the respiratory tract, which the authors believe to be initiated by a virus, as to prevent superimposed pulmonary infection caused by these organisms Although the final figures in the study speak well for the effectiveness of such vaccines in lowering the morbidity rate, they are not completely convincing Unfortunately, as the authors admit, the alternate method of vaccinating every other man in a given group to evaluate the effectiveness of a vaccine was not practiced Instead, the results observed in certain groups of vaccinated miners were compared with those in

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17 Bullowa, J G M, and Mayer, E The Hazards of the Induction of Pneumothorax in the Treatment of Lobar Pneumonia, *J A M A* **105** 191-193 (July 20) 1935 Bullowa, J G M Pneumothorax in Pneumonia An Appraisal, *New York State J Med* **35** 1001-1018 (Oct 15) 1935

18 Abernethy, T J, Horsfall, F L, and MacLeod, C M Pneumothorax Therapy in Lobar Pneumonia, *Bull Johns Hopkins Hosp* **58** 35-58 (Jan) 1936

19 Lister, S, Ordman, D, and Peall, P A The Epidemiology of Pneumonia on the Witwatersrand Goldfields and the Prevention of Pneumonia and Other Allied Acute Respiratory Diseases in Native Labourers in South Africa by Means of Vaccine, *Pub South African Inst M Research* **7** 1-124 (April) 1935

groups of unvaccinated workers from different mines. Conclusions must therefore be drawn with caution, since, as the authors state on page 30 "One of the most remarkable features of pneumonia on the Witwatersrand is its unequal occurrence from mine to mine."

Ross<sup>20</sup> found that the oral ingestion of types I, II and III pneumococcus vaccines caused protective antibodies to appear in from 60 to 75 per cent of persons. No specific agglutinins were demonstrable. Similar protective antibodies occurred naturally in from 10 to 50 per cent of unvaccinated persons. Finland and Ruegsegger<sup>21</sup> succeeded in producing antibodies in high titer in patients who received subcutaneous injections of 1 mg of the type-specific carbohydrate of pneumococci of type VIII. The carbohydrate of type III organisms was less effective. Cross-immune reactions between the two related types occasionally occurred.

*Nephritis in Pneumonia*—Numerous observers in the past have noted the relative infrequency of nephritis during pneumonia<sup>22</sup>. Transient albuminuria frequently occurred, and renal changes of a degenerative nature were commonly noted. Many observers, including myself, have never encountered clinical nephritis associated with pneumococcal lobar pneumonia. Interest in the matter was renewed since the publication of the studies of Blackman and Rake made several years ago. These authors noted acute nephritis in 9 per cent of children who died from pneumococcal infection but failed to observe it in adults. Seegal<sup>23</sup> recently studied 7 patients with acute nephritis among 1,004 adults with pneumococcal pneumonia, an incidence of 0.7 per cent. The nephritis developed in from two to three weeks after the onset of pneumonia.

*Pneumococcal Peritonitis*—Several studies of pneumococcal peritonitis have appeared during the year. King,<sup>24</sup> Tompkins<sup>25</sup> and Drachter<sup>26</sup> report several cases of pelvic infection in women caused by

20 Ross, V. Human Immunization Against Pneumococcus, *J Immunol* **27** 307-314 (Sept.) 1934.

21 Finland, M., and Ruegsegger, J. M. Immunization of Human Subjects with the Specific Carbohydrates of Type III and the Related Type VIII Pneumococcus, *J Clin Investigation* **14** 829-832 (Nov.) 1935.

22 Reimann, H. A. Acute Lobar Pneumonia, in Piersol, G. M., Bortz, E. L., and others. *The Cyclopedia of Medicine*, Philadelphia, F. A. Davis Company, 1934, vol. 9, p. 1059.

23 Seegal, D. Acute Glomerulonephritis Following Pneumococcal Lobar Pneumonia. Analysis of Seven Cases, *Arch Int Med* **56** 912-919 (Nov.) 1935.

24 King, J. E. Pneumococcus Pelvic Infection in Adults, *Am J Obst & Gynec* **29** 341-349, 1935.

25 Tompkins, P. Pneumococcus Pelvic Infection in Women, *Am J Obst & Gynec* **31** 70-78 (Jan.) 1936.

26 Drachter, R. Pneumokokkenperitonitis, *Ztschr f arztl Fortbild* **32** 620-625, 1935.

pneumococci and mention a number of other cases reported in the literature. Although most observers have considered the genital tract as the most frequent source or path of infection, these authors feel that many cases are preceded by acute disease of the respiratory tract which permits entry of pneumococci into the blood stream. The prognosis is good when the infection is localized in the pelvis and can be surgically drained. The prognosis is unfavorable when general peritonitis exists. Adequate drainage appears to offer the only hope for recovery. King and Tompkins believe that the respiratory tract is the portal of entry of infection and this view is substantiated by Schaanning's<sup>27</sup> study. Of 56 cases of pneumococcic peritonitis, in 16 the condition was preceded by pneumonia, in 7 by sore throat and in 2 by otitis media. In only 4 instances did the infection appear to originate from the pelvic organs. In the few cases in which the pneumococci were typed, type I was found seven times and types II, III and IV once each. The mortality rate among 35 children was 31 per cent. All of 14 adult patients died. It appeared that operation in the acute stage was unwise, since the mortality rate was 73 per cent, whereas the rate with expectant treatment was 31.6 per cent. Kramár<sup>28</sup> suggests that pneumococcic peritonitis is more common in children than is generally believed and cited 2 of his own "abortive cases." Many cases probably occur, but recovery follows without the diagnosis of the condition. In many cases the condition is probably regarded as due to simple digestive disturbances. The diagnosis can be made only by abdominal paracentesis and bacteriologic examination of the exudate.

*Pneumococcus Toxin*—Petith<sup>29</sup> recently summarized the literature concerning toxins of the pneumococcus. He points out the complexity of the problem and the divergence of opinion. It has not been possible as yet to determine the rôle played by any of the described substances in actual infection. More studies have recently been made. In one<sup>30</sup> it was shown that small doses of the toxin obtained from autolysates of pneumococci grown anaerobically kill mice. It was possible to prepare an antitoxin against this substance. Coca<sup>31</sup> also reported a toxin pro-

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27 Schaanning, C. K. Ueber Pneumokokkenperitonitis, Acta chir. Scandinav. **77** 256-270 (Nov. 15) 1935.

28 Kramár, J. Ueber die abortive Form der Pneumokokkenperitonitis, Monatschr. f. Kinderh. **61** 370-373 (March 15) 1935.

29 Petith, H. Eine kritische Studie über die Rolle der Pneumokokkentoxine im immunbiologischen Bilde der Pneumokokkenkrankungen, Zentralbl. f. inn. Med. **55** 97-118 (Feb. 3) 1934.

30 Weld, J. T., and Gunther, A. Effect of Anaerobically Prepared Pneumococcus Autolysate Toxin on Mice and Evaluation of Pneumococcus Autolysate Antitoxin in Mice, J. Exper. Med. **62** 119-127 (July) 1935.

31 Coca, A. F. A Study of the Pneumococcus Toxins, J. Immunol. **30** 1-32 (Jan.) 1936.

duced by the growth of pneumococci under certain atmospheric conditions. That toxin likewise was antigenic, but it was not composed of the specific polysaccharide. Subcutaneous injections of the toxin often caused high fever, anorexia, local swelling and discomfort. Immunity developed in children after a single injection of the toxin. The toxin could be neutralized by the serum of an immunized child but not by normal serum. About 95 per cent of patients convalescent from pneumonia showed negative results of skin tests when the toxic filtrate was injected. The toxin appeared to be type specific. For example, a person immunized with toxin produced from type I pneumococci reacted weakly to type I toxic filtrate but strongly to the filtrate obtained from other types. These observations, if they can be confirmed, are obviously of considerable significance.

#### INFLUENZA

The knowledge gained from the highly important investigations on influenza discussed in several previous reviews<sup>32</sup> has been extended by a number of interesting studies. Francis and Magill<sup>33</sup> have found that the rabbit, which is apparently not susceptible to infection after inoculation with the virus of influenza, nevertheless shows specific antibodies in the serum which serve to protect mice against intranasal infection with the virus. Subcutaneous or intraperitoneal injection of the virus into mice also fails to produce symptoms of infection in these animals, but mice so treated are actively immunized against subsequent infection by the intranasal route, which otherwise causes disease. Strains of influenza virus obtained from patients in widely separated groups were found to be immunologically related to each other but were not identical with the virus of swine influenza. The same investigators<sup>34</sup> vaccinated 10 persons subcutaneously with virus grown in tissue culture. No constitutional symptoms were noted. The procedure caused the development or increase of specific protective substance in 9 of the subjects. Several reports<sup>35</sup> of the cultivation of the virus in vitro

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32 Klotz, O., and Holman, W. L. Studies on Influenza, *Am J M Sc* **191** 426-446 (March) 1936. Reimann, H. A. Infectious Diseases. Review of the Current Literature, *Arch Int Med* **56** 382-411 (Aug.) 1935. Francis, T. Recent Advances in the Study of Influenza, *J A M A* **105** 251-254 (July 27) 1935.

33 Francis, T., and Magill, T. P. Immunological Studies with the Virus of Influenza, *J Exper Med* **62** 505-517 (Oct.) 1935.

34 Francis, T. and Magill, T. P. Vaccination of Human Subjects with Virus of Human Influenza, *Proc Soc Exper Biol & Med* **33** 604-606 (Jan.) 1936.

35 Francis, T., and Magill, T. P. Cultivation of Human Influenza Virus in an Artificial Medium, *Science* **82** 353-354 (Oct 11) 1935. Smith, W. Cultivation of the Virus of Influenza, *Brit J Exper Path* **16** 508-512 (Dec.) 1935.

have appeared. The virus was isolated during an epidemic of influenza in Australia by Burnet<sup>36</sup>

Andrewes, Laidlaw and Smith<sup>37</sup> in further studies showed that mice, contrary to expectations, could not be infected directly with washings from the throats of patients with influenza. Before mice could be infected the strains had to be passed through several ferrets. The authors found that the majority of normal persons possess neutralizing antibodies against influenza virus in their blood. They were unable to infect 2 human volunteers with ferret passage virus. The serum of each subject, however, contained neutralizing antibodies before the test was made. The size of the virus particles was estimated by filtration methods to be somewhat smaller than that of the viruses of vaccinia and herpes<sup>38</sup>. The minuteness renders it unlikely that the virus represents a small form of influenza bacillus or of any other bacterium which has been suggested as the causative agent of influenza. These authors, contrary to the experience of Noble and Bramard,<sup>39</sup> were unable to obtain a virus from patients with the common cold.

Dochez and his associates<sup>40</sup> inoculated human volunteers with the bacteria-free filtrate of nasopharyngeal washings from patients with influenza both of the epidemic and of the sporadic type. The type of infection evoked with virus from the sporadic type resembled the syndrome of the common cold rather than that of influenza. It was noted, however, that a more pronounced constitutional reaction occurred after inoculation with influenza virus than after inoculation with virus of the common cold. Volunteers were successfully inoculated with the virus after its cultivation *in vitro*. The presence of certain pathogenic bacteria commonly found in the upper respiratory tract was not observed to modify the character of the induced infection. The difficulty of differentiating the virus of the common cold from that of influenza was pointed out. The two viruses were thought to be closely related biologically.

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36 Burnet, F. M. Influenza Virus Isolated from Australian Epidemic, *M. J. Australia* **2** 651-653 (Nov. 9) 1935.

37 Andrewes, C. H., Laidlaw, P. P., and Smith, W. Influenza. Observations on the Recovery of Virus from Man and on the Antibody Content of Human Sera, *Brit. J. Exper. Path.* **16** 566-582 (Dec.) 1935.

38 Elford, W. J., Andrewes, C. H., and Tung, F. F. The Sizes of the Viruses of Human and Swine Influenza as Determined by Ultrafiltration, *Brit. J. Exper. Path.* **17** 51-53 (Feb.) 1936.

39 Noble, W. C., and Bramard, D. H. Note on Susceptibility of Ferrets to Virus of Common Cold, *J. Bact.* **29** 407-411 (April) 1935.

40 Dochez, A. R., Mills, K. C., and Kneeland, Y. Studies on the Virus of Influenza, *J. Exper. Med.* **63** 581-598 (April) 1936.

Brightman,<sup>41</sup> in studies involving the infection of ferrets with influenza virus obtained from children, noted the invasion of the lungs by hemolytic streptococci in about a third of his animals. The streptococci evidently originated in the ferret, since immunologically similar strains were found in normal ferrets. They seemed to be a secondary invader affecting animals after the resistance had been reduced by the influenza virus infection.

#### THE COMMON COLD

Dochez and his associates<sup>42</sup> report new observations on the bacteria-free filtrable virus of the common cold. They succeeded in cultivating the virus in a tissue culture medium, and they reproduced the disease in volunteers inoculated with this culture virus. Interesting observations were made concerning the presence of inclusion bodies in the epithelial cells of the upper respiratory tract in human beings.<sup>43</sup> These inclusion bodies were found more commonly in persons with a mild respiratory infection. The histologic structure and staining properties of the cytoplasmic inclusions, the authors believe, differentiate them from cell detritus or other artefacts. It is claimed that the inclusion bodies have been cultivated in tissues of the chick embryo.

At a recent meeting Kerr<sup>44</sup> stated that it does not seem necessary to assume that a virus plays any part in causing the common cold. Many patients with a "cold" do not show symptoms characteristic of infection. He believes that environmental changes, such as chilling, irritants and various vasomotor disturbances, cause the symptoms regarded as those of the common cold. He raises the question as to whether or not products of tissue culture other than a virus may not in themselves cause symptoms. I do not concur in this extreme view of Kerr. Beyond question symptoms of rhinitis may be produced by environmental changes, by various irritants and by other causes, but from clinical and epidemiologic observation and carefully controlled experiments it is well established that certain forms of the ill defined complex known as the common cold are definitely infectious and are caused by a transmissible virus. The few experiments cited by Kerr which resulted in failure to transmit the disease cannot be said to prove the noninfectious nature of the illness.

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41 Brightman, I J. Streptococcus Infection Occurring in Ferrets Inoculated with Human Influenza Virus, *Yale J Biol & Med* **8** 127-135 (Dec) 1935

42 Dochez, A R, Mills, K C, and Kneeland, Y. Studies on the Common Cold, *J Exper Med* **63** 559-579 (April) 1936

43 Broadhurst, J, Liming, R M, MacLean, M E, and Taylor, I. Cytoplasmic Inclusion Bodies in the Human Throat, *J Infect Dis* **58** 134-149 (March-April) 1936

44 Kerr, W J. The Common Cold, *J A M A* **107** 323 (Aug 1) 1936

During the past year two papers<sup>45</sup> have appeared concerning the use of "heterophile" antigen vaccine to be given by mouth for the prevention of colds. The vaccine contains pneumococci, influenza bacilli, streptococci and *Micrococcus catarrhalis*. In the face of much excellent evidence that the cold is caused by a filtrable virus, environmental changes and various other causes, it is difficult to understand the persistence of investigators in ignoring modern research in this regard. It is now generally believed that pneumococci or other organisms commonly found in the rhinopharynx may at times be responsible only for certain complications or sequelae of the cold. Furthermore, no one has as yet produced a vaccine for the common cold which is effective even when given by the subcutaneous route, which is the usual method of stimulating antibodies. Evidence that immunity is established when any vaccine is taken by mouth is vague even in the case of typhoid vaccine, which is highly effective when given subcutaneously. Furthermore, the statistical evidence used by the authors to demonstrate the effectiveness of oral heterophile vaccine is insufficiently controlled, too limited and unconvincing.<sup>46</sup>

#### ACUTE RHEUMATIC FEVER

Coburn and Pauli<sup>47a</sup> studied a group of children with rheumatic heart disease among whom occurred an epidemic of influenza complicated with *Streptococcus haemolyticus* infections. They believe that the influenza virus had no effect in reactivating rheumatic fever, but recrudescences occurred after the development of postinfluenzal streptococcic infections due to a single strong toxin-producing strain of *Str. haemolyticus*. None of the 7 children who escaped streptococcic infection showed rheumatic symptoms, 14 of the 17 who were infected suffered a relapse of rheumatic fever. In another study<sup>47b</sup> they found a close relationship between streptococci causing scarlet fever and those causing rheumatic fever as regards the production of toxin and streptolysin. Neither active nor passive immunization to hemolytic streptococci was found to inhibit the development of rheumatic infection. These observations suggested to the authors that the immune response of the

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45 Rockwell, G. E., Van Kirk, H. C., and Powell, H. M. Oral Immunization to Colds, *J. Immunol.* **28** 475-484 (June) 1935, Further Studies on Oral Immunization to Colds, *Science* **82** 177-178 (Aug. 23) 1935.

46 Thomson, D., Thomson, R., and Thompson, E. T. Immunization by the Oral Route in Respiratory Infections, *Brit. M. J.* **1** 258-261 (Feb. 8) 1936. Rockwell, Van Kirk and Powell<sup>45</sup>.

47 Coburn, A. F., and Pauli, R. H. Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process, (a) *J. Exper. Med.* **62** 129-136, 137-158 and 159-169 (Aug.) 1935, (b) *J. Clin. Investigation* **14** 755-762, 763-768, 769-781 and 783-791 (Nov.) 1935.



host plays an important rôle in the development of the disease. Infection with certain streptococci initiates a process peculiar to rheumatic subjects, that is, a substance which alters mesodermal tissues is released when an immune response to the streptococci occurs.

While these studies and many previous ones have incriminated infections caused by hemolytic streptococci in inciting a relapse of rheumatic fever, recent observations<sup>48</sup> show that other factors also are of importance. While Bland and Jones admit that infection of the respiratory tract precedes 75 per cent of the observed recurrences, they show that in the remaining 25 per cent there was no preceding infection of the respiratory tract. Furthermore, tonsillitis and pharyngitis were not consistently followed by the recurrence of rheumatic fever in likely subjects. In their experience other forms of infection, injection of anti-typhoid vaccine, accidents involving fractured bones or sprained joints and surgical operations also have appeared to reactivate a latent rheumatic infection or have raised the asymptomatic phase of rheumatic fever to a clinical level.

The same authors<sup>49</sup> made a study concerning the significance of chorea in rheumatic fever. They point out that although chorea appears to be a manifestation of rheumatic fever, the positive proof of the etiologic relationship is controversial and awaits further study. Over a period of eight years 72 per cent of 482 patients with chorea exhibited other signs of rheumatic fever, in 28 per cent chorea alone was found. Heart disease occurred in 73 per cent of those with both rheumatic fever and chorea but in only 3 per cent of those with chorea alone. Death occurred in 17 per cent of patients with chorea alone, as compared with 14 per cent of those with other rheumatic symptoms. Chorea therefore appears to be a mild manifestation of rheumatic disease not often followed by the usual serious consequences.

Two studies<sup>50</sup> confirm the close relationship between rheumatic activity and changes in the sedimentation rate of the blood. Acute chorea prompted only a slight, transient increase. In rheumatic fever the sedimentation rate closely paralleled the activity of the disease and led the authors to regard the test as valuable in following the progress of the disease. An increase in the rate indicated reactivation of the virus.

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48 Bland, E. F., and Jones, T. D. Clinical Observations on the Events Preceding the Appearance of Rheumatic Fever, *J. Clin. Investigation* **14** 633-648 (Sept.) 1935. Edstrom, G. Mechanisches Trauma und nachfolgende Febris rheumatica, *Acta med. Scandinav.* **88** 342-353, 1936.

49 Jones, T. D., and Bland, E. F. Clinical Significance of Chorea as a Manifestation of Rheumatic Fever, *J. A. M. A.* **105** 571-577 (Aug. 24) 1935.

50 Payne, W. W., and Schlesinger, B. A. Study of the Sedimentation Rate in Juvenile Rheumatism, *Arch. Dis. Childhood* **10** 403 (Dec.) 1935. Wood, P. The Erythrocyte Sedimentation Rate in Diseases of the Heart, *Quart. J. Med.* **5** 7 (Jan.) 1936.

or increasing severity of the disease, while a decreasing rate was of good prognostic import. Although the continued activity of the disease is almost always accompanied by an abnormally high rate, I do not believe that an increased rate invariably indicates continuation of the infection. In cases of lobar pneumonia, for example, the sedimentation rate may be increased for weeks after the crisis and may be the last measurable factor to return to normal.

Several studies on the etiology of rheumatic fever have been published recently. Schlesinger and his associates<sup>51</sup> were able to detect particles which resembled the elementary bodies of vaccinia, psittacosis and varicella when rheumatic exudates and suspensions of infected tissues were centrifugated at high speed. These bodies when suspended in suitable fluids were agglutinated specifically by the serums of patients with acute rheumatic infections. No agglutination occurred in serum from patients in whom the infection was quiescent or in serum from normal persons. They suggest that in rheumatic fever the streptococcus causes an infection and prepares the soil, so to speak, for the growth of the virus. Coles<sup>52a</sup> reports the demonstration of similar bodies in acute rheumatic fever and in rheumatoid arthritis but also in 50 per cent of pericardial fluid from patients with other conditions as well. Aschoff<sup>52b</sup> regards the work of Schlesinger as of great significance but believes that the virus is the primary cause of the disease and that the streptococcus is a secondary invader. If Aschoff's view, which is held by many, is correct, it is striking how differently streptococcal infection becomes manifest in rheumatic fever as compared with its behavior as a complication of influenza.

Before regarding these studies too seriously, the recent work of Logrippo<sup>53</sup> must be considered. This investigator, studying the so-called "globoid bodies" of poliomyelitis, found that opalescence and micrococcal forms developed in culture mediums both with and without the presence of virus. He showed that the establishment of an electrical field caused tissue lipoids to pass into suspension and to react to stains similar to the forms observed in virus culture. The physical state of certain fluids, he believes, can well account for the stable emulsion that

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51 Schlesinger, B., Signy, A. G., Amies, C. R., and Barnard, J. E. Aetiology of Acute Rheumatism. Experimental Evidence of a Virus as the Causal Agent, *Lancet* **1** 1145-1149 (May 18) 1935.

52 (a) Coles, A. C. Virus Bodies in the Pericardial Fluid of Rheumatic Fever and Other Conditions and in Joint Fluid of Rheumatoid Arthritis, *Lancet* **2** 125-126 (July 20) 1935. (b) Aschoff, L. Ueber den spezifischen infektiösen Rheumatismus, *München med. Wchnschr.* **82** 1597-1598 (Oct. 4) 1935.

53 Logrippo, G. A. Concerning the Nature of the Globoid Bodies, *J. Bact.* **31** 245-253 (March) 1936.

is being interpreted as growth. Nevertheless, other recent studies<sup>54</sup> have shown that the elementary bodies of vaccinia contain ash, carbohydrate, fat and nitrogen similar to other substances of protoplasmic origin.

#### UNDULANT FEVER (BRUCELLIASIS, BRUCELLOSIS)

The annual increase in the number of recognized and reported cases of undulant fever since 1924 has led many to regard it as a new and spreading disease<sup>55</sup>. However, as old records are searched descriptions of maladies are found which resemble undulant fever in many respects and make it seem almost certain that the disease has existed in this country for many years. Interpretations of old reports must, however, be accepted with caution, as illustrated by an article on certain aspects of the life of Lincoln<sup>56</sup>. It appears that in 1818 Lincoln's mother, Nancy Hanks, contracted and died from a disease known as "milk-sick" which swept southern Indiana in epidemic form. It was thought at the time that the disease was passed to human beings in cow's milk. Many cows aborted. At present this epidemic is believed by some to have been a variety of undulant fever. There are, however, several factors opposed to this view. Undulant fever seldom occurs in an explosive epidemic, and it is not characterized by a mortality rate as high as that reported in the 1818 outbreak. Recent investigations have confirmed the opinion of the pioneers in regard to snake-root in fodder as the cause of the disease. This herb causes "trembles" in cattle and is often fatal. The poison is transmissible to human beings through the milk.

The publication of numerous clinical descriptions and epidemiologic studies<sup>57</sup> on undulant fever during the past year or two indicate widespread interest in the disease. Reviews of the disease as it appeared in Scotland, England, Sweden and elsewhere have been published and a congress on brucellosis was held in France. Unfortunately, little actual advance in knowledge has been made.

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54 Hughes, T. P., Parker, R. F., and Rivers, T. M. Immunological and Chemical Investigations of Vaccine Virus, *J. Exper. Med.* **62** 349-352 (Sept) 1935.

55 Roth, F. Ueber den Infektionsmodus, die latente Infektion und die Ursache der Häufigkeitszunahme der Bangschen Erkrankung des Menschen, *Ztschr. f. klin. Med.* **126** 507-534 (April) 1934.

56 Carskadon, T. R. Mother of Lincoln, *Delineator*, February 1936, p. 51.

57 Beattie, C. P., Smith, J., and Tulloch, W. J. Undulant Fever in Scotland, *Lancet* **1** 1427-1431 (June 22) 1935. Dalrymple-Champneys, W. Undulant Fever, with Especial Reference to Its Clinical Aspects in England and Wales, *ibid.* **2** 1449-1453 (Dec. 28) 1935. Olin, G. Studies on Undulant Fever in Sweden, *Svenska Lak-sällsk. handl.* **61** 63-168, 1935. Harris, H. J. Undulant Fever. Difficulties in Diagnosis and Treatment, Preliminary Report of Fifty-One Cases, *New York State J. Med.* **34** 1017-1021 (Dec. 1) 1934. The First Reported Case of Undulant Fever, foreign letter, *J. A. M. A.* **105** 1366 (Oct. 26) 1935.

Many clinical reports have recently appeared describing unusual cases or complications which, while largely new to the medical profession in the United States, were for the most part observed and described years ago by British army surgeons in Malta. Meningitis due to *Brucella* has been reported in several papers <sup>58</sup>. One patient who recovered was treated with injections of toxic filtrate of cultures of *Brucella* and by frequent copious drainage of the spinal fluid <sup>58b</sup>. Marietta <sup>58d</sup> collected reports of several cases in which the condition was characterized by meningeal and osseous involvement and added a report of a case of his own. Cases of undulant fever associated with pneumonia as an outstanding feature were reported by Johnson and Bogart <sup>59</sup>. Krohmann <sup>60</sup> reports a case in which hematemesis occurred, which he believes may have resulted from ruptured esophageal varices secondary to hepatic cirrhosis and splenomegaly in a youth of 26. He suggests that prolonged (two years) infection may have caused the cirrhosis. Similar cases are reported by Diehl and Roth <sup>61</sup>. Cases in which cholecystitis and hepatitis also were present are reported in other papers <sup>62</sup>. Spondylitis also has been observed <sup>63</sup>.

Several studies emphasize the prevalence of infection, latent or otherwise, in the population as a whole, as evidenced by the frequency of positive results of serum agglutination and cutaneous tests. It is said that agglutinins and specific cutaneous sensitivity develop only when there has been invasion of tissues by the living *brucella* organism followed by the actual disease or inapparent, symptomless infection, as discussed in subsequent paragraphs. Heathman <sup>64</sup> studied the agglutinin

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58 (a) Bingel, A, and Jacobsthal, E. Meningitis in *Alcaligenes Abortus* Infection, *Klin Wchnschr* **12** 1093-1095 (July 15) 1933. (b) Hartley, J A, and Millice, G S. Undulant Fever Meningitis, *J A M A* **103** 251-253 (July 28) 1934. (c) Hardy, A V, Borts, I H, and Jordan, C F. Undulant Fever in Iowa, *Tr A Am Physicians* **49** 93-99, 1934. (d) Marietta, S U. Involvement of the Spinal Meninges and of Bone in Undulant Fever Simulating Tuberculosis, *Am Rev Tuberc* **32** 257-284 (Sept) 1935.

59 Johnson, R M. Pneumonia in Undulant Fever, *Am J M Sc* **189**: 483-487 (April) 1935. Bogart, F B. Pulmonary Changes in Undulant Fever, *South M J* **29** 1-8 (Jan) 1936.

60 Krohmann, L. Ein bemerkenswerde Fall von Morbus Bang mit Magendarmblutungen, *Munchen med Wchnschr* **81** 1268-1269 (Aug 17) 1934.

61 Diehl, F, and Roth, F. Hepatohenale Syndrome bei Bangscher Krankheit, *Deutsches Arch f klin Med* **178** 271-288, 1935.

62 (a) MacQuiddy, E H, and Martin, J W. Cholecystitis Due to *Brucella Melitensis*, *Nebraska M J* **19** 227 (June) 1934. (b) Mettier, S R, and Kerr, W J. Hepatitis and Cholecystitis in the Course of *Brucella* Infection, *Arch Int Med* **54** 702-710 (Nov) 1934.

63 Snyder, C H. Spondylitis in Undulant Fever. Report of Two Cases, *J Michigan M Soc* **34** 224-228 (April) 1935. MacQuiddy and Martin <sup>62a</sup>.

64 Heathman, L S. A Survey of Workers in Packing Plants for Evidence of *Brucella* Infection, *J Infect Dis* **55** 243-265 (Nov-Dec) 1934.

and dermal reactions of employees in meat packing plants. She found a divergence in the incidence of the allergic state and the presence of agglutinins. Eighty per cent of the employees in contact with fresh blood and tissues showed allergic responses in contrast with 55 per cent in the group as a whole. Only 8.4 per cent of all the employees showed significant agglutinins, a figure close to that noted by other investigators. Agglutinins were present in about the same percentage of workers exposed to fresh tissues as of those not exposed to infection. The high percentage of persons in the allergic state indicated that the cutaneous test as a diagnostic aid must be used with caution, especially when the results of the agglutination test and blood cultures are negative. Heathman's results seemed to show that the high incidence of positive cutaneous reactions of those most exposed to fresh blood and tissues may be the result of numerous and repeated exposures to *Brucella*, which perhaps caused symptomless or subclinical infection. Workers handling beef are almost constantly exposed to infection but rarely show symptoms of clinical infection, whereas among the pork handlers exposure is less frequent but when it occurs infection more often reaches the clinical stage. The author believes that the agglutination and cutaneous reactions alone are not reliable criteria of the degree of infection. Conversely, other observers have noted that from 10 to 16 per cent of the patients with undulant fever fail to have agglutinins. Goldstein<sup>65</sup> recommends the cutaneous test only as a supplementary diagnostic procedure. Favorite and Culp<sup>66</sup> present more evidence to show that the intradermal test is specific.

As remarked in a preceding paragraph, many studies indicate the widespread nature of the disease<sup>67</sup>. Evidences of previous infection, as registered by the presence of agglutinins and a positive result of the cutaneous test in an otherwise healthy person, are frequently noted in persons with no history of infection with *Brucella*. It appears, then, that while a large portion of the population are repeatedly exposed to infection with *Brucella*, a certain proportion are apparently resistant to infection or receive subinfective doses while others, with less resistance, show signs and symptoms of the disease in widely divergent gradations. Some, although actually infected (symptomless infection, as evidenced by the presence of agglutinins and cutaneous sensitivity), never show signs or symptoms, some show symptoms so mild as to be unrecog-

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65 Goldstein, J. D. Cutaneous Reactions in the Diagnosis of Undulant Fever, *J Clin Investigation* **13** 209-218 (March) 1934

66 Favorite, G. O., and Culp, C. F. The Intradermal Test in Undulant Fever, *J Lab & Clin Med* **20** 522-526 (Feb.) 1935

67 (a) Evans, A. E. Chronic Brucellosis, *J A M A* **103** 665-667 (Sept 1) 1934. (b) Scoville, W. F. The Prevalence of Mild *Brucella Abortus* Infections, *ibid* **105** 1976-1977 (Dec 14) 1935. Roth<sup>55</sup>

nizable clinically, some manifest typical signs and symptoms which comprise the typical clinical entity of undulant fever, and a few apparently have little or no resistance and rapidly succumb to overwhelming infection. There is no evidence to show that virulence per se of the infecting micro-organism is responsible for the variations in the degree of severity of the illness, the greatest variable seems to involve the host, the macro-organism (Meyer<sup>68</sup>). These views are illustrated in reports of epidemics in two institutions. In both the source of the contaminated milk was known. In one study<sup>69</sup> of 300 elderly inmates, all whom undoubtedly ingested the contaminated milk, 35 per cent of those tested gave evidence of symptomless infection by the presence of specific serum agglutinins, but only 14 actually showed symptoms which lasted for from four to forty weeks. Three of the patients died. The other report<sup>70</sup> concerns an epidemic among 210 children, all of whom drank milk infected with *Brucella melitensis*, variety *suis*, in which only 14 per cent of those tested showed agglutinins for this organism, only 13 per cent showed positive cutaneous reactions and only 2 showed manifestations of the disease. When the contaminated milk was withdrawn the agglutinins disappeared rapidly, but the cutaneous reaction was strongly positive and in some cases continued to be positive.

Two papers deal especially with low grade, often afebrile undulant fever. Because a certain number of patients with mild but prolonged infection with *Brucella* (chronic brucellosis) complain of exhaustion, insomnia, irritability and aches and pains for which no objective signs can be found, they are apt to be regarded as neurasthenic or neurotic. Evans<sup>67a</sup> suggests that patients with such a train of vague symptoms should always be tested for the presence of agglutinins and the cutaneous reaction to *Brucella*. Since both these tests are often unreliable, efforts should be made to cultivate the organism from the blood or excretions, a procedure admittedly difficult and unlikely to be successful in cases of low grade infection. Exception may be taken to Evan's conclusion that "clinical diagnosis is extremely difficult even in severe cases." Undulant fever in my experience has been relatively easy to detect, especially when sought for. The symptoms, signs and laboratory findings in the average case are usually characteristic.

Scoville<sup>67b</sup> records his own case in which the condition was characterized by a prolonged afebrile course. The condition was considered as due to neurasthenia or chronic neutropenia until proved to

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68 Meyer, K. F. Latent Infections, *J. Bact.* **31** 109-135 (Feb.) 1936

69 Horning, B. G. Outbreak of Undulant Fever Due to *Brucella suis*, *J. A. M. A.* **105** 1978-1979 (Dec. 14) 1935

70 McBryde, A., Daniel, N. C., and Poston, M. A. *Brucella* Infection in Children, *J. Pediat.* **4** 401-405 (March) 1934

be undulant fever after five months, when the result of a cutaneous test was found to be strongly positive. Agglutinins were absent. Of interest also is the record of a normal sedimentation rate of the erythrocytes. This is contrary to what is typical of most infections, and it appears to be a characteristic peculiar to undulant fever, as pointed out by Curschmann<sup>71</sup>

The treatment of undulant fever is dealt with in a comprehensive review<sup>72</sup>. The authors conclude that a successful method still awaits development. No therapeutic agent has as yet been found which has been proved to alter to a significant degree the natural course of the disease. They believe that the beneficial effects accruing from whatever therapy is used are due to nonspecific systemic reactions, an opinion in which I concur. The surprisingly few studies of the influence of specific immune serum therapy in experimentally infected animals have not been encouraging<sup>73</sup>.

Several experimental studies are of interest. Feldman<sup>74</sup> detected agglutinins in 10 per cent of 500 dogs but was unable to cultivate *Brucella* from any. Attempts<sup>75</sup> to convert bovine strains into porcine strains by passage of bovine strains of *Brucella* through hogs were unsuccessful<sup>75</sup>. The *Brucella* are pathogenic for white mice<sup>76</sup>.

A general review of the pathology of undulant fever was published by Sharp<sup>77</sup>. Wight<sup>78</sup> discusses the program for a nation wide campaign to control the disease in cattle. It is proposed to slaughter all cattle with specific agglutinins in the serum. Thus far it is estimated that about \$25 a head will be paid for the animals destroyed.

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71 Curschmann, H. Ueber die diagnostische Bedeutung der Senkungsreaktion bei akuten Infektionskrankheiten, *Munchen med Wchnschr* **80** 1767-1768 (Nov 10) 1933

72 Carpenter, C. M., and Boak, R. A. The Treatment of Human Brucellosis. A Review of Current Therapeutic Methods, *Medicine* **15** 103-127 (Feb) 1936

73 Gwatkin, R. *Brucella Abortus* Infection in Guinea Pigs. Prevention and Treatment with Immune Serum, *J Infect Dis* **53** 230-236 (Sept-Oct) 1933  
Beach, B. A. The Influence of Bovine Serum on *Brucella* Infections in Guinea Pigs, *ibid* **56** 38-40 (Jan-Feb) 1935

74 Feldman, W. H., Mann, F. C., and Olson, C. The Spontaneous Occurrence of *Brucella* Agglutinins in Dogs, *J Infect Dis* **56** 55-63 (Jan-Feb) 1935

75 Gilman, H. L., Milks, C. H., and Birch, R. R. Passage of Bovine *Brucella* Through Swine, *J Infect Dis* **54** 171-174, 1934

76 Singer, C., and Shaw, E. B. *J Bact* **29** 44 (Jan) 1935. Feldman, W. H., and Olson, C. The Pathogenicity of *Brucella Abortus* for White Mice, *J Infect Dis* **57** 212-222 (Sept-Oct) 1935

77 Sharp, W. B. Pathology of Undulant Fever, *Arch Path* **18** 72-108 (July) 1934

78 Wight, A. E. The Nationwide Campaign to Control Bang's Disease, *J Am Vet M A* **87** 291-295 (Sept) 1935

## TUBERCULOSIS

A number of important experimental studies of tuberculosis have been made. Derick, Branch and Crane<sup>79</sup> found it difficult to diminish in animals the hypersensitivity to tubercle bacilli. The best method employed a heat-killed vaccine. The life of infected animals was prolonged after the use of such an antigen. In the course of their work the investigators tested their own sensitivity to tuberculin. One who had had tuberculosis failed to react, while another who had never had active tuberculosis reacted vigorously. The experience made them doubtful of the clinical value of the tuberculin test as regards diagnostic problems in individual cases, a feeling which I share. The frequency with which the reaction is negative in clinically proved cases of tuberculosis and positive when active tuberculosis cannot be demonstrated renders the test as reliable or as unreliable as any other test of this kind. The test is no doubt valuable when applied to large numbers of supposedly healthy persons for the purpose of detecting cases of subclinical transmissible tuberculosis.

Oppenheimer<sup>80</sup> produced a lesion which was similar to that of so-called epituberculosis (benign, resolving preliminary tuberculosis of childhood) by introducing dead tubercle bacilli intratracheally into hypersensitive rabbits. When living bacilli were injected, progressive tuberculosis developed. It was suggested that epituberculosis is caused by the erosion of a bronchus by a caseous lymph node which liberates tuberculoprotein and dead bacilli into the lungs of sensitized and immunized persons.

Clawson<sup>81a</sup> studied the relation of allergy to the presence of lesions in animals vaccinated with BCG. He found that in animals made allergic and subsequently inoculated with living or heat-killed BCG extensive tuberculosis developed. Normal animals inoculated with BCG rarely showed pathologic changes. It appeared that the allergic state caused a marked increase in the susceptibility to the development of lesions. The experiments further supported the belief that no allergy exists without tuberculous lesions.

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79 Derick, C. L., Branch, E. A. G., and Crane, M. P. Attempts to "Desensitize" Tuberculous Guinea Pigs with Dead Vaccine and Products of Tubercle Bacillus, *Am Rev Tuberc* **32** 218-228 (Aug) 1935.

80 Oppenheimer, E. H. Experimental Studies on the Pathogenesis of Epituberculosis, *Bull Johns Hopkins Hosp* **57** 247-276 (Nov) 1935.

81 Clawson, B. J. (a) Relation of Allergy and Lesions in Animals Vaccinated with BCG, *Arch Path* **19** 673-678 (May) 1935, (b) Experiments Relative to Vaccination Against Tuberculosis with the Calmette-Guérin Bacillus (BCG), *ibid* **20** 343-368 (Sept) 1935, (c) Destruction of Tubercle Bacilli Within Phagocytes in Vitro, *J Infect Dis* **58** 64-69 (Jan-Feb) 1936.



The same investigator<sup>81b</sup> noted that guinea-pigs and rabbits vaccinated with BCG were protected against infection with strains of virulent tubercle bacilli. Both subcutaneous and intravenous injections of living or heat-killed BCG organisms were found to be efficacious. The injection of living organisms intravenously is not considered a safe method, however. Allergic reactions were produced in sensitive animals. Animals vaccinated intravenously with heat-killed organisms did not become allergic. Clawson does not believe that allergy which develops in the course of subcutaneous vaccination is especially harmful or dangerous. In another paper Clawson<sup>81c</sup> reports on the demonstration *in vitro* of lysis of tubercle bacilli in the presence of immune serum. Lysis occurred much more slowly in normal serum. Mononuclear leukocytes of immune and allergic animals when washed free from serum appeared to be more effective in bringing about lysis than normal leukocytes. From these observations it is suggested that lysis of tubercle bacilli is probably a natural method of combating and destroying the organisms in a tuberculosis-infected body, yet Krause in 1926 presented experimental evidence which weighed against any interpretation which would make immunolyses decisively responsible for the results observed.

Scheel,<sup>82</sup> of Oslo, reports that the morbidity among students working with tuberculous patients is higher than that among the general population. His studies indicated that students with negative results of cutaneous tests showed a morbidity three times as high as that shown by those with positive results of cutaneous tests. BCG vaccine is said to have greatly reduced the morbidity rate among students with negative results of cutaneous tests. These views are at variance with many recent studies which purport the existence of hypersensitivity or allergy to render the liability to reinfection greater. I believe that the dangers of allergy as a liability to tuberculosis in the human subject have been exaggerated.

Smithburn,<sup>83</sup> studying the morphology of colonies of tubercle bacilli, concluded that virulence is associated usually with the number of organisms present and with the proportion of S types in the culture. Not all S forms are virulent. He believes that the native resistance of the rabbit is associated with a power to dissociate inoculated S bacilli into rough (R) forms and then destroy them. This power is not possessed by the naturally susceptible guinea-pig. I am skeptical whether rabbits actually possess a "power" to enforce dissociation. Many other observers have failed to demonstrate any connection between microbic dis-

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82 Prevention of Tuberculosis in Medical Students with BCG Vaccine, foreign letter, *J A M A* **105** 1925 (Dec 7) 1935

83 Smithburn K C The Colony Morphology of Tubercle Bacilli, *J Exper Med* **62** 645-663 (Nov ) 1935

sociation and recovery from infection Smithburn's observations may, however, be the first to demonstrate the occurrence Besta,<sup>84</sup> in studying the same problem, was unable to detect the profound biologic changes between the S and the R forms of tubercle bacilli, such as are noted among certain other bacteria

Studies<sup>85</sup> have been made on the waxes of tubercle and leprosy bacilli The unsaponifiable fractions of these organisms, though extremely stable chemical compounds and insoluble in water, are remarkable stimulants of cells They give rise to the production of new monocytes which fuse into giant cells, surround the wax and engulf it The waxes are then slowly disintegrated without damage to the cells They have no effect on the resistance of the host

An excellent series of studies showing the importance of familial infections and the danger of infection to those exposed to tuberculosis has been published by Opie and his associates<sup>86</sup> Opie<sup>87</sup> also summarizes the present concepts of tuberculous infection and disease Michelson<sup>88</sup> reviews the literature concerning the primary complex of tuberculosis of the skin and adds 2 case reports of his own

#### MENINGITIS

Numerous outbreaks of localized epidemics of meningococcic meningitis during the past year have prompted the publication of several pertinent studies Neal<sup>89</sup> points out the frequency of the disease in infants under 1 year of age and the difficulties of diagnosis unless the spinal fluid is examined or blood cultures are made She advises conservatism in serum therapy and recommends the injection of 20 cc of serum intraspinally once in twenty-four hours after drainage of the subarachnoid space Spinal drainage should be repeated at intervals of from twenty-four to forty-eight hours to relieve pressure Tillett and Brown<sup>90</sup> studied a series of 21 cases, in which there was only 1

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84 Besta, B Untersuchungen über die "Dissoziation" von Tuberkelbacillen, *Ztschr f Hyg u Infektionskr* **117** 403-425 (Nov) 1935

85 Sabin, F R, Smithburn, K C, and Thomas, R M Cellular Reactions to Waxlike Materials from Acid Fast Bacteria, *J Exper Med* **62** 751-769 and 771-786 (Dec) 1935

86 Opie, E L Present Concepts of Tuberculous Infection and Disease, *Am Rev Tuberc* **32** 617-630 (Dec) 1935

87 Opie, E L, and McPhedran, F M Organization of Out-Patient Tuberculosis Clinic for Epidemiological Investigation, *Am J Hyg* **22** 539-658 (Nov) 1935

88 Michelson, H E The Primary Complex of Tuberculosis of the Skin, *Arch Dermat & Syph* **32** 589-601 (Oct) 1935

89 Neal, J B Meningococcic Meningitis in Children, *J A M A* **105** 568-571 (Aug 24) 1935

90 Tillett, W S, and Brown, T M Epidemic Meningococcus Meningitis, *Bull Johns Hopkins Hosp* **57** 297-316 (Nov) 1935

death All the patients received serotherapy intravenously and intraspinally The authors emphasize the value of spinal drainage in itself The low mortality rate in this series is in striking contrast with that reported by Tripoli<sup>91</sup> (65 per cent of 221 cases) Tripoli points out how unsatisfactory therapeutics of bacterial meningitis is in general In a study of 468 cases, classified etiologically, the mortality rate from meningitis caused by bacteria other than meningococci was 98 per cent I am of the opinion that the mortality rate would be considerably lower if spinal puncture and examination of the spinal fluid were made and reported in every case of suspected meningitis Conklin<sup>92</sup> discusses the difficulties of making diagnoses in cases of atypical meningococcic infection without meningeal involvement

In classifying cases of meningitis the diagnosis should be confirmed by cultural and serologic methods In forms other than tuberculous meningitis or meningitis due to *Torula*, morphologic identification by stained preparations is unreliable and insufficient Cocci ordinarily gram-positive may, if dead, be decolorized Two cases of meningitis said to have been due to the pneumococcus in which a cure was obtained are reported,<sup>93</sup> but the diagnosis was based only on examination of slides of stained preparations Reports of this kind are unacceptable and misleading Without bacteriologic studies of the solubility in bile and a determination of the type, the pneumococcus often cannot be differentiated from certain other gram-positive cocci

A method by which meningococcic meningitis can be diagnosed quickly is urgently needed It is common practice to administer anti-meningococcus serum as soon as gram-negative cocci are found in stained smears of spinal fluid, which is perhaps justifiable considering the imperfection of tests in current use Much serum is no doubt wasted, and perhaps some harm is done, since other coccic invaders of the meninges may be gram-negative It is not possible to identify bacteria with certainty on the basis of morphologic or tinctorial characteristics alone Furthermore, the type-specificity among meningococci renders the use of homologous type-specific therapy imperative Since positive identification by cultural methods is too time consuming, it is hoped that some test like the precipitin reaction, as proposed by Rake,<sup>94</sup>

91 Tripoli, C J Bacterial Meningitis, *J A M A* **106** 171-175 (Jan 18) 1936

92 Conklin, C B Meningococcemia, *M Ann District of Columbia* **4** 313-315 (Dec) 1935

93 Meyer, P R Pneumococcic Meningitis, *J A M A* **105** 1844-1845 (Dec 7) 1935 Smith, H R Pneumococcic Cerebrospinal Meningitis with Recovery, *ibid* **105** 1845 (Dec 7) 1935

94 Rake, G Studies on Meningococcus Infection, *J Exper Med* **58** 375-383 (Sept) 1933

will solve the problem. He<sup>95</sup> recently discussed the problem in the epidemiology of type-specific meningococci.

Scott, Rivers and Armstrong<sup>96</sup> studied cases of bacteria-free acute lymphocytic choriomeningitis in which a virus was recovered from the spinal fluid. Although the patients had no contact with one another, the viruses were found to be identical or closely related. In last year's review<sup>97</sup> these results were shown to be open to some criticism on the basis of the work done by Traub, who found a similar virus in mice which he said he believed was the natural host or source of the virus. The recent studies by Rivers and Scott, however, definitely demonstrate that the virus isolated by them was derived from the patient's spinal fluid. It was immunologically identical with the virus of Armstrong and Lillie and with that of Traub. In regard to diagnosis, they point out the confusing fact that signs of meningitis may be the only clinical manifestation of a mild abortive attack of any one of a number of diseases, including poliomyelitis, the St. Louis type of encephalitis and epidemic encephalitis. Furthermore, signs of meningeal involvement may be the outstanding feature of other virus diseases, such as herpes zoster and mumps. An incorrect diagnosis in many cases is therefore likely to be made unless an effort is made to determine the etiologic agent in each instance.

#### POLIOMYELITIS

The possible danger and futility of vaccinating human subjects with recently developed poliomyelitis vaccines, as pointed out in last year's review, were discussed in a recent symposium<sup>98</sup>. Several authorities, especially Rivers and Leake, strongly deprecate the use of vaccines, as proposed by Brodie and by Kolmer. Rivers traces the development of knowledge in regard to vaccination against virus diseases and recalls that killed virus vaccine is ineffective as an antigen and that living virus, while antigenically effective, may produce the disease. Leake<sup>99</sup> recently reported 12 cases in which poliomyelitis developed after vaccination.

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95 Rake, G. Some Features of the Epidemiology of Meningococcus Meningitis, *Canad. Pub. Health J.* **27** 105-110 (March) 1936.

96 Scott, T. F. M., and Rivers, T. M. Meningitis in Man Caused by a Filterable Virus, *J. Exper. Med.* **63** 397-414 and 415-432, 1936. Armstrong, C., and Lillie, R. D. Experimental Lymphocytic Choriomeningitis of Monkeys and Mice Produced by a Virus Encountered in Studies of the 1933 St. Louis Encephalitis Epidemic, *Pub. Health Rep.* **49** 1019-1027 (Aug. 31) 1934. Armstrong, C., and Dickens, P. F. Benign Lymphocytic Choriomeningitis (Acute Septic Meningitis), *ibid.* **50** 831-842 (June 21) 1935.

97 Reimann, H. A. Infectious Diseases, *Arch. Int. Med.* **56** 382-411 (Aug.) 1935.

98 Symposium on Poliomyelitis, *Am. J. Pub. Health* **26** 95-112 (Feb.) 1936.

99 Leake, J. P. Poliomyelitis Following Vaccination Against This Disease, *J. A. M. A.* **105** 2152 (Dec. 28) 1935.

against the disease. In regard to the same problem Flexner<sup>100</sup> has shown that no evidence is at hand to prove that the treatment of virus with chemicals causes "attenuation." Such treatment either kills the virus or merely reduces or dilutes its concentration, the virulence of that which remains alive is unchanged. When the virus is destroyed it is no longer antigenic, when it is simply diluted it may immunize some animals and cause paralysis in others.<sup>101</sup> Second attacks have been reported to occur among human beings, and monkeys artificially immunized have been successfully reinfected.<sup>102</sup> No evidence exists to show, as claimed by some, that passage of the virus through monkeys removes its power to infect and produce paralysis in man. The use of poliomyelitis vaccine was recently forbidden in California.

Lennette and Hudson<sup>103</sup> cite the work reported since that of Flexner and Lewis in 1910 pertinent to the upper respiratory tract as a portal of entry and of the olfactory nerves as the route by which the virus reaches the central nervous system. They confirm previous observations that transection of the olfactory nerves prevents infection with virus administered intranasally. Similar obstruction to the entrance or passage of virus has been attained by the instillation of various chemicals into the nasal passages before inoculation.<sup>104</sup> Experiments of this type are designed to discover a safe and effective agent to be used as a prophylactic in epidemics of poliomyelitis. Attempts to isolate the virus from the nasopharynxes of human beings were not entirely successful.<sup>105</sup> The virus was recovered in only 1 of 26 cases.

Jungeblut<sup>106</sup> has demonstrated "poliocidal" substances of low titer in the tears of normal adult persons. Normal human saliva and spinal

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100 Flexner, S. Concerning Active Immunization in Poliomyelitis, *Science* **82** 420-421 (Nov 1) 1935

101 Olitsky, P., and Cox, H. R. Experiments on Active Immunization Against Experimental Poliomyelitis, *J. Exper. Med.* **63** 109-125 (Jan.) 1936

102 Flexner, S. Second Attacks and Reinfection in Poliomyelitis, *Science* **83** 487 (May 22) 1936

103 Lennette, E. H., and Hudson, N. P. Relation of Olfactory Tract to Intravenous Route of Infection in Experimental Poliomyelitis, *Proc. Soc. Exper. Biol. & Med.* **32** 1444-1446 (June) 1935

104 Armstrong, C., and Harrison, W. T. Prevention of Experimental Intranasal Infection with Certain Neurotropic Viruses by Means of Chemicals Instilled into Nostrils, *Pub. Health Rep.* **51** 203-215 (Feb. 21), 241-244 (March 6) 1936  
Schultz, E. W., and Gebhardt, L. P. Prevention of Intranasally Inoculated Poliomyelitis in Monkeys by Previous Intranasal Irrigation with Chemical Agents, *Proc. Soc. Exper. Biol. & Med.* **34** 133-135 (March) 1936

105 Paul, J. R., Trask, J. D., and Webster, L. T. Isolation of Poliomyelitis Virus from the Naso-Pharynx, *J. Exper. Med.* **62** 245-257 (Aug.) 1935

106 Jungeblut, C. W. Occurrence of Poliocidal Substances in Tears, Saliva and Cerebrospinal Fluid of Normal Individuals, *Proc. Soc. Exper. Biol. & Med.* **32** 1534-1537 (June) 1935

fluid were devoid of protective power. Surprisingly, the spinal fluid of monkeys convalescent from poliomyelitis contained no virucidal substances, while such substances were often present in the serum of the same animal.

In another paper Flexner<sup>107</sup> shows that after the nasal instillation of the virus of poliomyelitis monkeys may or may not manifest clinical symptoms but changes invariably develop in the spinal fluid. An increase in the number of cells often occurs within forty-eight hours after inoculation. The cell count is usually higher in animals in which paralysis has developed. Instillations of virus do not lead to active immunity unless clinical symptoms are produced. When no symptoms develop, no antibodies appear in the blood, and the animal is as susceptible to cerebral inoculation as a control monkey. A monkey which has had mild symptoms is immune, and its blood possesses antiviral substances. Essentially similar observations are reported by Jungeblut<sup>108</sup>. If the facts gained by these studies are applied practically, many epidemiologic problems regarding subclinical infection and the evidence of immunity frequently found in normal persons become understandable. As Flexner points out, however, it should be remembered that monkeys probably react differently to the virus than do human beings.

#### TULAREMIA

The frequency of pulmonary involvement in tularemia is discussed by several observers. Blackford<sup>109</sup> cites the literature on the subject and a description of 7 cases of tularemia pneumonia, 7 cases of tularemia associated with bronchitis and 3 cases of tularemia with pleural effusion which occurred in 35 cases of tularemia. He emphasizes how frequently the thoracic viscera were affected and shows that pulmonary or pleural involvement was detected in 50 per cent of cases of severe disease by clinical examination and in 90 per cent by roentgenographic studies. The presence of pulmonary involvement in cases of atypical manifestations, especially those of the "typhoid" type, is attended with diagnostic difficulties, and a diagnosis of tuberculosis or atypical pneumonia may be made unless the disease is kept in mind or other helpful evidence is obtained from a history of contact infection or by labora-

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107 Flexner, S. The Effects of Nasally Instilled Virus of Poliomyelitis in the Cerebrospinal Fluid and Blood of Monkeys, *J. Exper. Med.* **62** 787-804 (Dec.) 1935.

108 Jungeblut, C. W. On the Mechanism of Immunity in Experimental Poliomyelitis, *J. Infect. Dis.* **58** 150-157 (March-April) 1936.

109 Blackford, S. D. Pulmonary Manifestations in Human Tularemia, *J. A. M. A.* **104** 891-895 (March 16) 1935.

tory methods Roentgenographic studies are described in another paper <sup>110</sup> Bernstein <sup>111</sup> collected pathologic data from 18 necropsy reports of fatal cases of tularemia. He added 3 of his own cases of tularemia with pneumonia, in which complete necropsy studies were made.

Amoss and Sprunt <sup>112</sup> review reports of several instances of tularemia contracted by the ingestion of undercooked infected rabbit meat and add reports of 2 cases of their own in which the condition was possibly due to the same cause. Here again, in this type of case, the clinical course may be atypical, and the diagnosis may be difficult unless the history is carefully taken and appropriate laboratory tests are made. During the past year I have encountered three examples of unusual sources of infection, one the bite of a playful dog, one a scratch inflicted by a cat and one the bite of a captured field mouse which caused an interdigital ulcer. No other organism is known to inhabit so many different species of animals, birds and insects as *Pasteurella tularensis*.

Foshay <sup>113</sup> continues to report favorable results obtained in patients treated with specific antiserum. He says that reports of 240 cases in which serum treatment was given and 138 cases in which it was not given show that the duration of the symptoms is shortened by 50 per cent by the serum therapy and that the incidence of suppurative adenitis is lowered but that the duration of fever is not significantly altered. The mortality among the patients who did not receive serum was from 6 to 8 per cent, as compared with 2.5 per cent among those who were treated.

#### TETANUS

Two more important contributions on tetanus have appeared from Professor Abel's laboratory containing reports of investigations designed to prove that tetanus toxin is distributed by the blood stream and is not transmitted via the nerves to the central nervous system. By a number of convincing experiments <sup>114</sup> it is shown that when a minute dose of toxin is injected directly into the sciatic nerve of a dog no symptoms develop if precautions are taken to preclude leakage of the substance into the surrounding tissues. The same small dose, however, when injected into muscle suffices to produce pronounced local rigidity, but when injected intravenously it becomes so diluted and bound to other tissues as

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110 Archer, V. W., Blackford, S. D., and Wissler, J. E. Pulmonary Manifestations in Human Tularemia, *J. A. M. A.* **104** 895-898 (March 16) 1935.

111 Bernstein, A. Tularemia, *Arch. Int. Med.* **56** 1117-1135 (Dec.) 1935.

112 Amoss, H. L., and Sprunt, D. H. Tularemia, *J. A. M. A.* **106** 1078-1080 (March 28) 1936.

113 Foshay, L. On the Treatment of Tularemia, *Ohio State M. J.* **31** 21-24 (Jan.) 1935.

114 Abel, J. J., Hampil, B., and Jonas, A. F. Researches in Tetanus, *Bull. Johns Hopkins Hosp.* **56** 317-336 (June) 1935.

to be innocuous. The experiments show that so-called local tetanus is the result of the direct effect of the toxin on the involved muscles and is not due to the influence on the central nervous system. Abel believes that tetanus toxin acts powerfully in a direct manner on all voluntary muscles that have an intact motor nerve terminal, irrespective of the paths by which it reaches them.

The second paper <sup>115</sup> is devoted to historical notes on the pathogenesis of tetanus. The objections to using so "impractical and dangerous" a drug as magnesium sulfate to lessen the convulsions and the disappointing results obtained from the use of other hypnotics are pointed out. Furthermore, since every stage of contracture, inclusive of the terminal one, appears to be due not to an action of toxin on the central motor nuclei but to its direct action on the muscles themselves, the antitetanus serum now available is powerless to prevent the appearance or to retard the process of muscle contractures once the muscles have absorbed the toxin. There is no logic in the use of intraspinal injections of antitoxin either prophylactically or therapeutically.

Doerr <sup>116</sup> has not been able to confirm Abel's results fully. In a number of experiments he showed that the theory of the transportation of toxin exclusively by the blood stream fails to account for certain of the results observed in his experimental animals.

#### STREPTOCOCCIC INFECTION

Lyons <sup>117</sup> studied the effect of immunotransfusion on infections with hemolytic streptococci. He believes that these organisms produce disease by virtue of their ability to invade the body tissues and by their capacity to form toxins. The septic manifestations are characterized by cellulitis, abscess, inflammation, suppuration, remittent fever, chills and septicemia and the toxic element, by erythema, continuous fever and tachycardia. While I believe that the author overemphasizes the importance of phagocytosis in recovery from infection, one must agree with him that sufficient knowledge is at hand to warrant the therapeutic application of specific antitoxin and antibacterial serum. It is pointed out that because of the diversity of immunologic types of streptococci, <sup>118</sup>

115 Abel, J. J., and Hampil, B. Researches in Tetanus, *Bull. Johns Hopkins Hosp.* **67** 343-376 (Dec.) 1935.

116 Doerr, R., and Seidenberg, S. Dynamische Aktivierung des toxisch induzierten lokalen Tetanus, *Ztschr. f. Hyg. u. Infektionskr.* **117** 561-569 (Dec.) 1935. Doerr, R., Seidenberg, S., and Magrassi, F. Kritische und experimentelle Studien zur Frage des Nachweises von Tetanus Toxin in peripheren Nerven, *ibid.* **118** 92-116 (March) 1936.

117 Lyons, C. Immunotransfusion and Antitoxin Therapy in Hemolytic Streptococcus Infections, *J. A. M. A.* **105** 1972-1975 (Dec. 14) 1935.

118 Swift, H. W., Lancefield, R. C., and Goodner, K. The Serologic Classification of Hemolytic Streptococci in Relation to Epidemiologic Problems, *Am. J. M. Sc.* **190** 445-453 (Oct.) 1935.



commercially prepared polyvalent antistreptococcus serums were found not to possess specific antibodies for his own strains. In his paper methods are described for the selection of a human donor whose blood may contain specific antibodies for the strain of hemolytic streptococcus in question. The patient is then given a transfusion of blood from a suitable donor to combat the sepsis and to neutralize the toxin.

The complexity of the problem of infection and immunity in streptococcal infection is portrayed in studies on erysipelas by Keefer and Spink.<sup>119</sup> They believe that recovery from this infection results from a summation of a number of responses which tend to localize the infection or limit bacterial multiplication. The presence of antibodies which aid in phagocytosis and destruction of the organism seem to be of greatest importance in the process of recovery.

Hamman and Rienhoff<sup>120</sup> reported an interesting case of septicemia due to *Streptococcus viridans* which was first thought to be subacute bacterial endocarditis. No evidence of cardiac valvular lesions was found, however. The presence of an arteriovenous aneurysm of the external iliac artery and vein, acquired years before, led the authors to suspect that this defect was the focus of infection. That their surmise was correct was shown by the prompt disappearance of septicemia and the recovery of the patient after excision of the defect and by the demonstration of streptococci in the vegetations which partially occluded the opening which had formed between the artery and the aneurysmal sac. This case is an example par excellence of true focal infection. Instances of this type no doubt support the wave of enthusiasm extant regarding the teeth and tonsils, for instance, as foci of infection. Few concepts have so captured the imagination of the medical profession for so long as the theory of focal infection, yet here and there dissenting opinions are expressed. Hamman and Wainwright<sup>121</sup> point out the futility of the indiscriminate extraction of teeth and tonsils for the purpose of influencing general symptoms. Dawson<sup>122</sup> and I<sup>97</sup> have expressed similar views elsewhere.

The streptococcus has recently been incriminated by Rosenow and Butt as the cause of still another disease. Butt<sup>123</sup> studied several cases

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119 Keefer C S, and Spink W W. Studies of Hemolytic Streptococcus Infection, *J Clin Investigation* **15** 17-19 (Jan) 1936. Spink, W W, and Keefer, C S. *ibid* **15** 21-35 (Jan) 1936.

120 Hamman, L, and Rienhoff, W F. Subacute Streptococcus Viridans Septicemia, *Bull Johns Hopkins Hosp* **57** 219-234 (Oct) 1935.

121 Hamman L, and Wainwright, C W. Diagnosis of Obscure Fever, *Bull Johns Hopkins Hosp* **58** 109-133 (Feb) 1936.

122 Dawson, M H. Chronic Arthritis, in Nelson Loose-Leaf Living Medicine New York, Thomas Nelson & Sons, 1935.

123 Butt, H R. Myasthenia Gravis. Study of Postmortem Observations Including Demonstration of Gram-Positive Bacteria (Streptococci) in and Between Muscle Fibers. *Arch Path* **21** 27-34 (Jan) 1935.

of myasthenia gravis and noted collections of lymphocytes and streptococci in stained sections of muscle. It is suggested that these bacteria may be the origin of the toxin that produces the characteristic fatigability in this disease. In experimental studies cultures of streptococci obtained from these patients were shown<sup>124</sup> to produce lesions in the muscles of rabbits resembling the lesions of patients with myasthenia gravis. However, many of the lesions shown in the author's illustrations are characteristic of myositis and not of myasthenia gravis.

The ascribing of the power to cause disease to a few organisms present in diseased muscle is open to serious question. Observations by Reith<sup>125</sup> showed that cocci other than staphylococci existed in muscle tissues in 16 per cent of 108 samples from healthy hogs, rabbits and guinea-pigs. Burn,<sup>126</sup> studying human tissue post mortem, noted that nonhemolytic streptococci were the third most common organism present. The results of Reith and Burn would make it surprising if the ubiquitous nonhemolytic streptococci were not observed occasionally in muscular tissue, especially when diseased, as in myasthenia gravis. Lastly, one is led to speculate on the beneficial effects of the administration of amino-acetic acid which are said to be obtained in myasthenia gravis in relation to the streptococcus as an etiologic agent.

#### STAPHYLOCOCCIC INFECTION

A number of important contributions concerning staphylococci have appeared during the year. An outbreak of food poisoning due to staphylococci involving 206 persons was reported<sup>127</sup>. All the patients recovered within a few hours. Blackman<sup>128</sup> discusses an example of staphylococcic infection of the small intestine associated with septicemia. Death occurred within thirty-six hours. At autopsy, acute inflammation and many staphylococci were noted in the walls of the jejunum and part of the ileum. Rigdon<sup>129</sup> reports 7 cases of staphylococcic infection with evidence of renal damage. He believes that the thrombi present in the capillary loops may be the result of the necrosis and

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124 Rosenow, E. C., and Heilman, F. R. Bacteriologic Studies in Myasthenia Gravis, *Proc Soc Exper Biol & Med* **34** 419-425 (May) 1936. Boothby, W. Myasthenia Gravis. A Discussion of Its Etiology, read before the Association of American Physicians on May 5, 1936.

125 Reith, A. F. Bacteria in the Muscular Tissues and Blood of Apparently Normal Animals, *J Infect Dis* **12** 367-383, 1926.

126 Burn, C. G. Postmortem Bacteriology, *J Infect Dis* **54** 395-403, 1934.

127 Dack, G. M., Bowman, G. W., and Harger, R. N. An Outbreak of Food Poisoning Apparently Due to Staphylococci, *J A M A* **105** 1598 (Nov 16) 1935.

128 Blackman, S. S. Acute Staphylococcal Infection of the Jejunum and Ileum, *Bull Johns Hopkins Hosp* **57** 589-594 (Nov) 1935.

129 Rigdon, R. H. Renal Lesions in Staphylococcus Aureus Infections and Their Relation to Acute Glomerular Nephritis, *Arch Int Med* **57** 117-131 (Jan) 1936.

fusion of endothelial cells. The presence of erythrocytes in the glomerular spaces and of albumin, red cells and casts in the urine is the result of a toxin liberated by the staphylococci. The damage to the kidney is usually insufficient to produce clinical evidence of glomerulonephritis.

Important work on the classification of staphylococci is reported by Julianelle and Wiegard.<sup>130</sup> They find the agglutination test less reliable for this purpose than the precipitin test made with purified carbohydrate derivatives of staphylococci. With the latter test the organisms fell into two distinct types, those from infected human beings falling into type A and those from other sources into type B. Studies of this kind are necessary before the specific therapy of staphylococcic infections can be satisfactorily developed.

MacNeal and Frisbee<sup>131</sup> report the results of the use of bacteriophage in the treatment of 100 patients with staphylococcic bacteremia. Although 75 of these patients died, the authors state that the staphylococcic infection of the blood stream was definitely influenced and that bacteriophage is at times live-saving. Before one accepts the therapeutic value of bacteriophage for this type of infection, several points must be considered. In the first place, in order to evaluate its effectiveness, the results in patients with similar manifestations who have and those who have not received bacteriophage must be compared. To include cases in which there were serious primary conditions, like carbuncles, with those of simple bacteremia, obviously distorts the statistical analysis. For example, transitory bacteremia with staphylococci and other organisms was found in 16 of 51 patients after tonsillectomy by Fischer and Gottdenker,<sup>132</sup> who concluded that bacteremia of this type is not rare and seldom leads to serious consequence. Of MacNeal's 25 patients who received treatment and who recovered, there were many who apparently suffered from a mild infection, as far as can be gathered from the data given, and only 5 of these were over the age of 30. In Scott's<sup>133</sup> study of septicemia, the mortality rate among patients with staphylococcic sepsis not treated with bacteriophage was similar, 79 per cent. From an academic point of view, Evans has shown that bacteriophage is inactivated by blood, pus, ascitic fluid and saliva. No evidence exists of the lytic action of bacteriophage *in vivo*. Furthermore, the concentration after injection into the blood stream is far too weak to produce a lytic action, and finally there is as yet no unanimity

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130 Julianelle, L. A., and Wiegard, C. W. The Immunological Specificity of Staphylococci, *J. Exper. Med.* **62** 11-21 (July) 1935.

131 MacNeal, W. J., and Frisbee, F. C. One Hundred Patients with Staphylococcus Septicemia Receiving Bacteriophage Service, *Am. J. M. Sc.* **191** 179-195 (Feb.) 1936.

132 Fischer, J., and Gottdenker, F. Transitory Influx of Bacteria into the Blood Stream After Tonsillectomy, *Wien klin. Wchnschr.* **49** 177 (Feb. 7) 1936.

133 Scott, W. J. M. The Principles of the Treatment of Septicemia, *J. A. M. A.* **105** 1246-1249 (Oct. 19) 1935.

of opinion as to what bacteriophage really is. Until it is shown that recovery, when it does occur, is the result of the specific action of bacteriophage on the staphylococcus and is not due to the nonspecific shock which usually follows such treatment, the procedure must be regarded as purely experimental. Scott concludes that the most important principle in the treatment of septicemia in general is the eradication or exclusion from the circulation of foci that cause reinfection of the blood. No chemotherapeutic agent has been found to be of value. Transfusion is a supportive measure. The most hopeful line of progress, he believes, is the development of an immune serum specific for the infecting organism, which can be given early in the course of the septicemia.

#### RICKETTSIAL DISEASES

Parker<sup>134</sup> has published his results of ten years' experience in prophylaxis against Rocky Mountain spotted fever with vaccine. It was found that vaccine prepared by treating virus-laden adult wood ticks with a phenol-formaldehyde mixture evoked a significant degree of protection against the disease. The degree of immunity produced was usually sufficient to afford full protection against relatively mild strains and appeared to ameliorate the symptoms produced by virulent strains sufficiently to insure the recovery of the infected persons. Annual vaccination is recommended for those living in areas where the virulence of *Rickettsia* is known to be high. The dosage prescribed is two subcutaneous injections of 1 cc each for children under 10 and two or three injections of 2 cc each for adults.

Two investigators from Morocco<sup>135</sup> report the successful vaccination of natives against typhus by inoculating them with living virus treated with bile. Although the use of living virus as a vaccine is deprecated as a dangerous practice, no bad effects were mentioned. Other investigators<sup>136</sup> have protected guinea-pigs against the European louse-borne typhus with the serum of a horse immunized with killed *Rickettsia* of the Mexican flea-borne murine type, thus providing further evidence of the close relationship of the two forms. Further reports<sup>137</sup> of a similar relationship of typhus viruses in another part

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134 Parker, R. R. Rocky Mountain Spotted Fever. Results of Ten Years' Prophylactic Vaccination, *J Infect Dis* **57** 78-93 (July-Aug.) 1935.

135 Vaccination Against Typhus with a Living Virus, foreign letter, *J A M A* **105** 524 (Aug. 17) 1935.

136 Zinsser, H., Castaneda, M. R., and Hager, F. D. Protective Action of Concentrated Antityphus Serum (Murine Type) Against European Typhus Virus, *Proc Soc Exper Biol & Med* **33** 44-47 (Oct.) 1935.

137 (a) Lewthwaite, R., and Savor, S. R. The Typhus Group of Diseases in Malaya, *Brit J Exper Path* **17** 1-34 (Feb.) 1936. (b) Kligler, I. J., Aschner, M., and Levine, S. Comparative Studies of the Louse-Borne (Epidemic) and Flea-Borne (Murine) Typhus Viruses, *ibid* **17** 53-60 (Feb.) 1936. (c) Pijper A., and Dau, H. South African Typhus, *J Hyg* **35** 116-124 (Feb.) 1935.

of the world have appeared. Lewthwaite and Savoor<sup>137a</sup> have shown a relationship between so-called rural and urban (flea-borne) tropical typhus in Malaya. Pijper<sup>137c</sup> has shown that three forms of typhus-like diseases occur in South Africa: tick-bite fever, flea typhus and louse typhus.

These studies show that typhus is widely distributed throughout the world. The variety found in any given place may be modified by passage through different insect or animal hosts. Somewhat similar variations in Rocky Mountain spotted fever have been noted in this country. The so-called eastern and western strains vary in the clinical manifestations they produce and in their behavior in guinea-pigs. There is evidence that a third and even milder form exists in the midwestern states<sup>138</sup>. The widespread nature of the disease raises the question of abandoning the restrictive term Rocky Mountain. It would be better, perhaps, if this group of diseases were simply named tick fever or spotted fever. The latter term is less preferable, since it has long been applied to other infections.

Several studies on the Weil-Felix reaction have been carried on in Zinsser's laboratory. In one<sup>139</sup> it was found that about 15 per cent of serums from persons not suffering from infections gave the Weil-Felix reaction in a titer of 1:40 or 1:80. In a few instances the titer was as high as 1:160. Another study<sup>140</sup> apparently solved the riddle of the curious serologic relationship between *Rickettsia prowazekii* and *Bacillus proteus* X 19, which is the basis of the Weil-Felix reaction. Castaneda found that one of the two polysaccharides derived from *B. proteus* X 19 is immunologically similar to the antigenic factor in *R. prowazekii*.

A modern classification of human rickettsial disease is conveniently illustrated in the accompanying table prepared by Felix<sup>141</sup>.

#### MALARIA

In October 1934 an epidemic of malaria began in Ceylon which subsequently exceeded all previous ones in magnitude<sup>142</sup>. It reached its height in December 1934, abated somewhat until April 1935, when

138 Reimann, H. A. Rocky Mountain Spotted Fever in Minnesota, *Minnesota Med* **19** 343-346 (June) 1936.

139 Savoor, S. R., Castaneda, M. R., and Zinsser, H. Notes on the Weil-Felix Reaction in Individuals Not Suffering from Typhus, *Proc Soc Exper Biol & Med* **33** 365-366 (Dec) 1935.

140 Castaneda, M. R. The Antigenic Relationship Between *B. Proteus* X19 and *Rickettsia*, *J Exper Med* **62** 289-296 (Sept) 1935.

141 Felix, A. The Serology of the Typhus Group of Diseases, *Tr Roy Soc Trop Med & Hyg* **29** 113-118 (July) 1935.

142 The Ceylon Malaria Epidemic 1934-1935. Report by the Director of Medical and Sanitary Service, Colombo, 1935, p. 1.

another wave overwhelmed the whole area, and finally subsided in June. Of 3,100,000 persons in the so-called wet zone, approximately 1,500,000 were infected. There were 90,000 deaths, which was more than double the usual number of deaths from malaria in this section of the island. In other regions the death rate from malaria was about one-third more than usual. This unprecedented outbreak was attributed to abnormal weather conditions. In the wet zone the region is densely populated, the rivers are almost always full and the conditions are usually unfavorable for the breeding of *Anopheles* mosquitoes. In the so-called dry zone malaria is endemic. The season after April 1934 was unusually dry, so that many of the flowing streams became a series of puddles, which were somewhat replenished by light rainfalls in July and October,

*Typhus Group of Fevers (After Felix)*

	Subgroup		
	Type x 19	Type x K	Type Undetermined
Name of disease	Classic epidemic typhus Tabardillo Endemic typhus (Brill's) of United States, Australia, Greece, Syria, Manchuria, Malaya (shop typhus) and Toulon (fièvre nautique)	Japanese river fever (Tsutsugamushi fever of Japan, Malaya and Netherlands Indies) Malay scrub typhus Scrub typhus of East Indies	Spotted fever of Rocky Mountains Sao Paulo endemic typhus Fièvre boutonneuse Febbre errutiva Tiek bite fever of South Africa Epidemic and endemic typhus of South Africa
Vector	Lice and rat fleas	Mites	Ticks, lice and rat fleas
Reservoir of virus	Rate Man	Field mice and rats	Rodents Dogs Ticks? Man
Agglutination	x 19 +++ x 2 + x K —	x 19 — x 2 — x K +++	x 19 + x 2 + x K +

thus furnishing suitable pools for mosquito breeding. In Ceylon eighteen varieties of *Anopheles* are found, which breed only in the dry zone. The rarely encountered variety *Anopheles culicifacies* is found only in the wet zone. Conditions in the wet zone in 1934 were therefore ideal for the multiplication of *A. culicifacies*, which subsequently appeared in unprecedented numbers and apparently was responsible for the epidemic. The epidemic began in a small village and spread rapidly down stream and finally over the island. In certain isolated localities the death rate was eight times higher than usual. In children less than 5 years old the condition was especially fatal. Many deaths were due to complications. In cases in which there were symptoms of cerebral involvement, chiefly due to *Plasmodium falciparum* infection, the condition was often fatal. Dysentery and pneumonia occurred frequently. *Plasmodium vivax* was found in 62 per cent of cases, *P. falciparum* in 36 per cent and *Plasmodium malariae* in 1 per cent.

Quinine therapy was successful in general, but relapses frequently occurred. Quinine sulfate and quinine bisulfate were most commonly used. Plasmochin and atabrine were used only when conditions provided the opportunity for constant observation, because of the liability of untoward side-effects. When atabrine was used, two injections usually sufficed, but similar results were obtained also with two intramuscular injections of quinine hydrochloride. The impression was gained that relapses after the use of atabrine by mouth were less frequent than after long continued treatment with quinine and that both procedures were better than two parenteral injections of atabrine.

The details of this epidemic are related to illustrate what a profound influence meteorologic conditions may have on the development and spread of epidemic disease. In the case cited two of the three factors required for the outbreak of an epidemic were at hand, the reservoir of infection in chronic carriers and the susceptible hosts. The means for transmission of the micro-organism from the carriers to the hosts were lacking until weather conditions favored the breeding of mosquitoes. The outbreak calls to mind forcibly the dangers constantly confronting populations when the usual biologic equilibrium is upset by war, flood, drought or other catastrophes.

*Blackwater Fever* —Although blackwater fever is now generally recognized as being invariably associated with malaria, if not actually being malaria, Fernán-Núñez<sup>143</sup> claims that it is practically the one remaining tropical disease the etiology of which has not been definitely determined. He suggests that the disease is an allergic manifestation of malaria which quinine aids in precipitating. Previous views have held that in blackwater fever the red blood cells of a patient treated with large doses of quinine salts are unusually susceptible to intravascular lysis or that quinine salts act as lysins for red blood cells that are already weakened by the intravascular lysins incident to the disease. The recent work of Ponder and Abels<sup>144</sup> shows that quinine hydrochloride is a simple hemolysin in vitro. They believe it unlikely that quinine salts produce intravascular lysis, since the low concentration attained would not cause lysis even in a solution of sodium chloride. Quinine salts do, however, bring about a decreased resistance of the red blood cells and accelerate other intravascular lysins.

#### MISCELLANEOUS INFECTIONS

*Measles* —According to McKhann and Chu immune globulin obtained from the human placenta is effective as a prophylactic agent against

143 Fernán-Núñez, M. Blackwater Fever, *Ann Int Med* 9 1203-1212 (March) 1936

144 Ponder, E., and Abels, J. C. Effect of Quinine Hydrochloride on Resistance of Rabbit Red Cells. *Proc Soc Exper Biol & Med* 34 162-165 (March) 1936

measles The product is now commercially available, and its merits have been considered by the Council on Pharmacy and Chemistry of the American Medical Association,<sup>145</sup> which has decided to postpone recognition of the product until more evidence of its value is at hand Other studies<sup>146</sup> suggest the curative value of the substance An injection of 2 cc caused modification of the infection in 13 of 18 cases.

*Rabies*—In the city of New York in 1934 over 19,000 persons were bitten by dogs, and 44 per cent of the dogs tested were found to be rabid<sup>147</sup> It is surprising and disappointing to learn that there has been a steady increase in dog bites in New York and that the death rate from rabies, in spite of the use of prophylactic vaccine, has not been lowered in twenty-five years The Pasteur prophylactic method does not invariably protect the patient, as commonly believed Sixty fatal cases of rabies were reported in the United States in 1933 The best method of control of the disease lies in the muzzling, leashing or elimination of biting dogs and in placing the responsibility and liability on the owners of dogs Vaccination of dogs against rabies is still in the experimental stage

*Dengue*—Cheney<sup>148</sup> reports 6 cases of an unusual syndrome characterized by severe aching pains and a high, usually biphasic, fever lasting about a week, without symptoms of involvement of the respiratory tract or of leukocytosis He suggests that the disease is a new entity in California and closely resembles dengue The disease was reproduced in 4 other persons by inoculation of blood from a patient He suggests that pleurodynia may be a form of dengue According to the surgeon general's report for 1935, 2,000 cases of dengue occurred in Florida in 1934, 1,962 in Georgia and 1,072 in Alabama The actual number of cases is undoubtedly much larger, since many cases are not reported Incidentally, in the same report mention is made of 5,371 cases of smallpox in 1934, the smallest number reported since records have been kept

*Plague*—A rather alarming outbreak of plague among squirrels in California was recently reported by Kellogg<sup>149</sup> Many of the animals found dead showed evidence of pulmonary involvement, while others

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145 Preliminary Report of the Council on Pharmacy and Chemistry, J A M A **105** 510-512 (Aug 17) 1935

146 Levitas, I M Treatment, Modification and Prevention of Measles by Use of Immune Globulin (Human), J A M A **105** 493-496 (Aug 17) 1935

147 Oleson, R Control of Rabies in New York City, Pub Health Rep **50**: 1087-1106 (Aug 16) 1935

148 Cheney, G Appearance of a Dengue-Like Fever in Northern California, Arch Int Med **56** 1067-1096 (Dec) 1935

149 Kellogg, W H Rodent Plague in California, J A M A **105** 856-859 (Sept 14) 1935



apparently died from septicemia too soon for pulmonary lesions or other evidence of focal necrosis to develop Kellogg points out the potential danger of the outbreak, its widespread nature and the permanence of the plague problem on the Pacific coast According to the surgeon general's report, fatal cases of plague occurred in Oregon in May, and in Tulare County, Calif, in June 1934 Plague-infected rodents were found in Oregon and in Montana

A French investigator<sup>150</sup> reports success in vaccinating natives of Madagascar with living plague organisms While this procedure appears to be highly dangerous, he claims that no accidents occurred among 47,000 vaccinated natives The procedure was said to have reduced the death rate from plague materially

L T Wu<sup>151</sup> has recently published a detailed history of two Manchurian outbreaks of plague

*Anthrax*—Gold<sup>152</sup> reported 10 cases of anthrax which developed in persons working with goat hair imported from China and India Antianthrax serum seemed to be of benefit in causing the temperature and pulse rate to return to normal but without effect on the adenopathy In some cases bacilli were recovered from the lesion after the patient had apparently recovered

*Typhoid*—The first important advance in the experimental attack on typhoid in years was announced by Rake<sup>153</sup> He succeeded in enhancing the pathogenicity of typhoid bacilli for mice by inoculating them with mucin, which sometimes increased the virulence a million times By this means he was enabled to test the efficiency of immune serum from vaccinated persons in protecting mice from infection It was found that the Widal reaction of the serum did not run parallel with the protective power It was never positive except in serum containing protecting antibodies Two serums which afforded protection, however, did not contain agglutinins for the antigens used Rake believes that the protective test is more delicate for detecting serologic changes than the Widal reaction

*Crystalline Virus*—Highly important studies on the nature of diseases of plants (tobacco-mosaic disease) due to a filtrable virus were

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150 Vaccination Against Plague with a Living Virus, foreign letter, J A M A 105 1283 (Oct 19) 1935

151 Wu, L T Manchurian Plague Prevention Service, Memorial Volume, 1912-1932, Shanghai, China, National Quarantine Service, 1934

152 Gold, H Studies in Anthrax Clinical Report of Ten Human Cases, J Lab & Clin Med 21 134 (Nov) 1935

153 Rake, G Enhancement of Pathogenicity of Human Typhoid Organisms by Mucin, Proc Soc Exper Biol & Med 32 1523-1524 (June) 1935

made by Stanley<sup>154</sup> He succeeded in obtaining a crystalline protein from infected tobacco and tomato plants by fractionation of the globulin in the plant extract, which had the properties of the virus The substance formed fine needle crystals, it was precipitated by protein precipitants, and it reproduced typical mosaic disease when introduced into fresh plants Repeated recrystallization left the infective properties unchanged When the virus was injected into animals serum precipitins for solutions of crystals developed in dilutions up to 1:100,000 Animals immunized with crystals showed precipitins for the crystalline protein and for the juice of infected plants but not for the juice of normal plants

If it can be proved beyond doubt that none of the actual virus was carried over in the processes of recrystallization, this work is of great significance, and it supports earlier suggestions regarding the possibility that nonliving substances can multiply on living tissues to produce disease

#### BACTERIAL INVASION

Although many theories have been propounded to account for the invasion of the body by pathogenic bacteria, the subject is still obscure Experimenters during the past half century have devoted most of their attention to the life history and habits of various bacteria, and it is only within the past decade or so that the attention of numerous investigators has been concentrated on the actual conflict of bacteria with their hosts Attempts have been made to determine why some bacteria are at times invasive, how and where they invade, what changes occur in the host as a result of invasion and whether the so-called defensive mechanism of the host is a purposeful reaction developed against age old exposure to a given organism or whether man, for example, has survived because his tissues "happen" to react in a manner which renders the growth or existence of bacteria impossible

Among investigators actively interested in this field in recent years may be mentioned Gay, Schwartzman, Cannon, Rich, Goodner, Menkin, Duran-Reynolds, Robertson and many others Limitation of space prevents discussion of all but a few papers, even of those published during the past year

Much of the recent work has already been discussed by Menkin<sup>155a</sup> This author showed experimentally that virulent pneumococci when

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154 Stanley, W. M. Isolation of a Crystalline Protein Possessing the Properties of Tobacco-Mosaic Virus, *Science* **81**:644-645 (June 25) 1935, The Isolation of Crystalline Tobacco-Mosaic Virus Protein from Diseased Tomato Plants, *ibid* **83** 85 (June 24) 1936

155 Menkin, V. (a) Inflammation and Bacterial Invasiveness, *Am J M Sc* **190** 583-596 (Nov.) 1935, (b) Studies on Inflammation, *J Infect Dis* **58**:81-91 (Jan-Feb.) 1936, (c) A Summary of the Effect of Ferric Chloride in Tuberculous Rabbits, *Proc Soc Exper Biol & Med* **34** 262-266 (March) 1936

injected into normal skin rapidly diffuse and cause death from septicemia. If, however, the area into which bacteria were injected was first treated with some substance which caused local inflammation, the bacteria were then hemmed in by a mechanical barrier of thrombosed lymphatic vessels and coagulated plasma. The localization of bacteria *in situ* resulted in a prolongation of the survival of the host. In other experiments<sup>155b</sup> Menkin produced a local area of inflammation in the skin and subsequently injected certain substances intravenously. The injected substances accumulated at the established focus in the skin, which he believes was the result of increased permeability of the capillaries at the site of inflammation. This may be an important point in connection with localization of infection, since antibodies which are closely associated with globulins may thus diffuse through the injured capillaries and accumulate at the site of entry of bacteria. The author believes that the reaction noted explains in part, at least, the Schwartzman phenomenon (when a filtrate of certain pathogenic organisms is injected into an area of the skin of rabbits, the area becomes the site of an intense local reaction if twenty-four hours later more of the same filtrate is injected intravenously). Menkin believes the Schwartzman reaction is nonspecific and dependent on the principles just mentioned. The same author<sup>155c</sup> also demonstrated an accumulation of ferric chloride in tuberculous areas in rabbits after intravenous injections and a definite retardation of the disease. The study has been extended to clinical cases.

Menkin's experiments recall the conclusions of Krause, published in 1926, which showed that the inflammatory allergic reaction at the site of inoculation of tubercle bacilli caused a "fixation" of bacteria at the site of injection and delayed or prevented further invasion. In spite of much experimental evidence to the contrary, it has seemed to me that the views of Krause are largely correct. While it appears true that severe allergic response is harmful, its dangers seem to have been exaggerated. A certain degree of allergy may provide conditions favorable for the restriction of bacteria at the site of entry.

Another interesting study in regard to localization of bacteria was made by Nedzel,<sup>156</sup> who injected pituitrin to produce transient spasm and anoxemia in tissues of the central nervous system. He then injected bacteria intravenously and demonstrated their presence in the area involved in the pressor effects. The capillaries of these regions, it was assumed, became more permeable, sticky and dilated, thus retarding the blood flow and permitting the adhesion of the bacteria to the walls of the capillaries.

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<sup>156</sup> Nedzel, A. J. Pressor Reactions and Bacterial Localization in the Central Nervous System, *Proc Soc Exper Biol & Med* **34** 239-240 (March) 1936

Many experimenters in this field have employed pneumococci. Teale<sup>157</sup> claims that the initial clearance of pneumococci from the circulation in immune animals was accomplished solely by phagocytic cells and not by circulating antibodies, since none could be demonstrated. The chief factor in immunity, he believes, is the state of the tissues with regard to the infecting bacteria. Goodner and Miller<sup>158</sup> state that anti-pneumococcus serum owes its protective properties to (1) the specific neutralization of the capsular substance of the pneumococci, (2) agglutination of the bacteria to permit phagocytosis and (3) the sensitization of the organism, which favors intracellular digestion. Robertson<sup>159</sup> presents evidence to show the importance of macrophages in recovery from pneumonia. In histologic studies of lungs, lesions exhibiting a well developed macrophage system were regularly characterized by a relative infrequency of pneumococci as compared with other involved areas.

Other investigators place more emphasis on humoral immunity in contrast with cellular immunity, thus perpetuating the controversy which originated with Metchnikoff. It is probable that most of the views discussed here are essentially correct. The matter is infinitely complex, "the number of forces or factors involved in the production of the end result is very large. Infection represents a constant state of flux and the tendency in either direction toward a state of equilibrium is constantly influenced by numerous opposing forces, often confusingly inter-related."<sup>158</sup>

The views of Rich and McKee<sup>160</sup> do not support those of Teale. These investigators have shown that immunized rabbits rendered leukopenic by benzene are capable of localizing pneumococci at the site of infection in the absence of leukocytes, in contrast with normal unimmunized animals. The authors believe that the presence of humoral immune antibodies causes prompt clumping and localization before an inflammatory exudate has a chance to accumulate. This point is also used to minimize Krause's views regarding the importance of allergic reaction, since Rich believes the retardation of bacterial spread occurred before the tissue response could develop. Humoral antibodies therefore appear to prevent the immediate spread of bacteria by holding them

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157 Teale, F. H. Some Observations on the Relative Importance of the Reticulo-Endothelial Tissues and the Circulating Antibody in Immunity, *J Immunol* **28** 133-160, 1935.

158 Goodner, K., and Miller, D. K. The Protective Action of Type I Anti-pneumococcus Serum in Mice, *J Exper Med* **62** 375-391 (Sept.) 1935.

159 Robertson, O. H., and Uhley, C. G. Changes Occurring in the Macrophage System of the Lungs in Pneumococcus Lobar Pneumonia, *J Clin Investigation* **15** 115-130 (Jan.) 1936.

160 Rich, A. R., and McKee, C. M. A Study of the Character and Degree of Protection Afforded by the Immune State Independently of the Leucocytes, *Bull Johns Hopkins Hosp* **54** 277-314 (April) 1934.

fixed at the site where they lodge until phagocytic leukocytes gather and destroy them Robben's<sup>161</sup> results do not show that phagocytic activity, as observed in free cells of the peritoneal cavity, is a factor in successful resistance against experimental pneumococcic infection No differences in cellular response were noted in animals experimentally inoculated, whether death or recovery ensued Dixon and McCutcheon,<sup>162</sup> studying chemotropism, recently presented evidence to show that human polymorphonuclear leukocytes when reacting to attraction by bacteria in vitro travel at no greater rate than when moving at random Drinker and his associates<sup>163</sup> studied the effect of immune serum on pneumococci in the thoracic lymph According to their experiments pneumococci invaded the lymph and multiplied rapidly Immune serum may remove them from the blood, but it cannot attain sufficient concentration in the lymph to be effective The lymphatic glands, therefore, may serve as a source of reinfection unless the antibody content of the blood is constantly replenished The authors believe that additional factors, probably cellular in nature, also play a rôle in recovery

Several years ago I demonstrated the effect of a slight increase of viscosity on the enhancement of specific agglutination of pneumococci Solutions of acacia adjusted to a viscosity of about 5.6 caused marked clumping of pneumococci in vivo in the presence of antipneumococcus serum in amounts too small to be effective unassisted The experiments were planned to determine whether or not the increase in globulins and viscosity of the blood so commonly noted in infection has any significance in the process of recovery These observations have been confirmed and extended by Catron<sup>164</sup> Pneumococci suspended in solution of acacia and injected into animals caused death sooner than organisms suspended in saline solution, but in the presence of a small amount of immune serum the pneumococci were localized and destroyed The experiments are of interest when compared with those of Miller and of Rake, who show that meningococci or typhoid bacilli are much more invasive in a mucinous suspension than when suspended in broth It appears that a certain range of viscosity may act as a deterrent to bacterial spread, espe-

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161 Robben, F. J., Rich, G. T., and Fleisher, M. S. Studies on Spontaneous Recovery from Pneumococcic Infection in the Guinea-Pig, *Arch. Path.* **20** 46-63 (July) 1935

162 Dixon, H. M., and McCutcheon, M. Chemotropism of Leucocytes in Relation to the Rate of Locomotion, *Proc. Soc. Exper. Biol. & Med.* **34** 173-176 (March) 1936

163 Drinker, C. K., Enders, J. F., Shaffer, M. F., and Leigh, O. C. The Immigration of Pneumococci Type III from the Blood into the Thoracic Duct Lymph of Rabbits, and the Survival of These Organisms in the Lymph Following Intravenous Injection of Specific Antiserum, *J. Exper. Med.* **62** 849-860 (Dec) 1935

164 Catron, L. Studies in Bacterial Localization, *J. Exper. Med.* **61** 735-752 (June) 1935

cially in the presence of immune serum, but a markedly viscous menstruum seems to protect bacteria from antibodies or phagocytes and to provide conditions favorable for growth. Du Nouy<sup>165</sup> demonstrated a momentary increase in viscosity when the specific antigen was added to immune serum. The reaction was specific. Pesch and Damm<sup>166</sup> have demonstrated pneumococcal properties of human saliva which are most effective at body temperature and are weakened after heating to 56 C or after filtration. Pneumococci cultivated in saliva rapidly lost their virulence for mice, and occasional dissociation into avirulent forms occurred.

All the work on bacterial invasiveness and host response still leaves many facts unexplained, among them the observation that type-specific, unchanged virulent pneumococci may be recovered from the lung after the crisis of pneumonia when the patient is well and from the lesions of rabbits which survive experimental dermal infection (Goodner). Numerous other examples of the presence and survival of organisms at the site of infection after recovery of the host exist.

In a recent address Meyer<sup>68</sup> discussed the important question of latent and symptomless infections. The term "latent infection," he believes, should denote merely the presence of a pathogenic organism in or on the body against which there has been no reaction. A representative example may be the existence of typhoid bacilli in the intestinal tract of a healthy carrier who has never had typhoid. The condition of latency, he believes, is conditioned chiefly by the behavior of the host, although localization of the organism or other behavior of the pathogen may influence the course. The terms "symptomless" or "inapparent infection" should apply to that state when pathogens actually invade the blood or tissues after a certain incubation period, evoke immune reactions and finally disappear without the manifestation of clinical or anatomic symptoms or signs of illness in the host, in other words, the virus is distributed in the usual time, location and quantity as found in a given clinical infection, except that no clinical evidence of disease develops. It seems that a third grouping should be made to accommodate the so-called abortive infections, such as the mildest forms of scarlet fever without the rash, of poliomyelitis without paralysis and of typhus without the eruption. The various gradations of clinical manifestations of any given disease seem to be due not to fluctuations of virulence of the infecting organism but rather to differences in the resistance of the host, which may be dependent on genetic factors.

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165 Du Nouy, L. Immunological Reactions and Viscosity, *Science* **82** 254 (Sept 13) 1935

166 Pesch, K. L., and Damm, R. Ueber die bactericide und virulenzvermindernde Wirkung von Speichel auf Pneumokokken, *Ztschr f Hyg u Infektionskr* **118** 1-16 (March) 1936

Meyer believes that in the question of latent, symptomless or sub-clinical infection lies the key to the understanding of latent epidemization and of the rise and fall of certain epidemic diseases. One wonders whether or not the existence of latent or symptomless infections will perennially frustrate any completely successful attempts to control infectious disease.

Gowen<sup>167</sup> recently published a brief review of studies on genetic constitution as a factor in disease and showed how the development of pathologic changes is often an expression of the host's inheritance rather than of the variability of the pathogens. The segregation of specific genes for susceptibility and resistance to disease initiated by pathogens may be responsible for immunity, morbidity or mortality within an exposed population.

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<sup>167</sup> Gowen, J. W. Genetic Constitution as a Factor in Disease, *Sigma Xi Quart* **23** 103-117 (Sept.) 1935.

## Book Reviews

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**Diseases of the Thyroid Gland** By Arthur E Hertzler, M D , Chief Surgeon, Halstead Hospital, Professor of Surgery, University of Kansas With a chapter on **Hospital Management of Goiter Patients**, by Victor E Chesky, M D , Chief Resident Surgeon, Halstead Hospital Third edition Price, \$7 50 Pp 348, with 181 illustrations St Louis C V Mosby Company, 1935

To the internist it appears that thyroid disease has been regarded from a wholly surgical point of view One gets the impression that thyroid enlargement is a condition in which surgical intervention is always indicated and that medical management is to be considered only as a preoperative measure or, perhaps, until the surgeon decides on a convenient time to operate

Today such an attitude seems a bit irrational Surely some patients with thyroid enlargement live out their life expectancy with the thyroid undisturbed, and doubtless some die from causes other than thyroid disease It seems possible that some goiters may regress and disappear without untoward symptoms Frank thyrotoxicosis has been known to undergo spontaneous and permanent remission Such instances appear to be unknown to this author

The etiology of thyroid disease is still obscure, and this obscurity is not lessened by Hertzler's discussion He hesitates to state that deficiency of iodine produces simple goiter elsewhere than in Dayton, Ohio In the interest of accuracy, it should be pointed out that the work of Marine and Kimball was done at Akron, Ohio, and has been confirmed in many other localities

The discussion of the symptomatology of the hyperthyroid state is shrouded in much the same obscurity Apart from the well recognized symptoms of thyrotoxicosis, Hertzler sets out a group of symptoms so intangible and ambiguous that they would warrant a diagnosis of hyperthyroidism in almost any case of nervous instability This is particularly true in view of the fact that he considers an elevation of the metabolic rate unnecessary for diagnosis

In the author's opinion the treatment is entirely surgical His aversion to compound solution of iodine, U S P, except as an immediate preoperative measure, and his fear of the results of the long continued use of iodine seem unwarranted in the light of more recent investigation

When one approaches the subject of the surgical removal of the thyroid the picture is different Here Hertzler shows complete familiarity with a highly technical subject All varieties of surgical approach, the removal of abnormally placed glands, the manner of dealing with complications and the preoperative and postoperative care in the hospital are adequately dealt with

The book is well and profusely illustrated but, contains no bibliography

**Classical Contributions to Obstetrics and Gynecology** By Herbert Thoms Price, \$4 Pp 265, with 57 illustrations Springfield, Ill Charles C Thomas, Publisher, 1935

Few publishers have had the satisfaction of offering volumes of medical classics which approach in quality and enjoyment those which bear the mark of Charles C Thomas, Publisher The reception accorded "Classical Descriptions of Diseases," "Selected Readings in Pathology," and others undoubtedly influenced the publishers to add to the series

This book marks another venture into obstetric history for Herbert Thoms It is larger and more comprehensive than his chapters in "American Obstetrics" and is modeled to the pattern established by Major's "Classical Descriptions of



Diseases" It contains the more notable contributions to the two sciences of obstetrics and gynecology, in the original wording of their creators, with short biographic sketches of the contributors

The chapters are arranged so as to group the material into general subjects, and in these various groupings the essays are presented in chronological order As an example, the chapter on puerperal fever contains the writings of Hippocrates, Alexander Gordon, Charles White, Holmes, Semmelweis and Pasteur on this subject As the reader progresses he leaves Gordon, who first demonstrated the infectiousness of the condition, to find Holmes, who showed its contagiousness, with Semmelweis he traces the modes of transmission and finally reads the words of Pasteur describing the experiments which proved beyond question the source and nature of the disease and the organisms most commonly responsible for it

The names of a few physicians, such as Smellie, Harvey and Mauriceau, appear in more than one chapter, in accordance with the greatness of these men The biographic sketches are fairly complete, if their brevity is considered, and are amply sufficient for their purpose

The contributions to gynecology are all contained in one short chapter This subject has been slighted for its older associate, obstetrics Papers by McDowell, Nathan Smith, Atlee, Sims, Tait, Wells and Noeggerath are included

No living authors are represented, and no material written since 1900 is used This, in part, may explain the shortness of the chapter devoted to gynecology Future generations will, no doubt, add many names, well known in the past thirty-five years, to the author's list

**The Treatment of Acute Poisoning** By H L Marriott, M D, Resident Medical Officer, The Middlesex Hospital, London Price, 5 shillings Pp 57, with 15 illustrations London John Murray, 1935

This is a delightful monograph, with an index deliberately omitted because the book is intended to be read as a whole, describing to the practitioner what measures to follow when he is confronted with a patient who is acutely poisoned

The author, a resident medical officer for eight years in the Middlesex Hospital, has had much practical experience in the management of such cases He writes naturally and easily of what the experience has taught him and describes in detail the treatment which he has found successful The illustrations are a not unimportant factor in making the book more readable

Any one who picks up the book will read it at one sitting and with enjoyment It should be made part of the standard equipment of any accident room

**Die seröse Entzündung** By Hans Eppinger, Hans Kaunitz and Hans Popper Price, 26 marks Pp 298, with 124 illustrations and 41 tables Berlin Julius Springer, 1935

In this monograph is assembled a large collection of data from the literature and from the authors' experimental work, dealing with the question of shock The subject then is elaborated to include general questions of the permeability of membranes To be fully appreciated the text must be carefully studied, and, while one may not agree with every detail, Eppinger's brilliant thinking is always instructive

# Archives of Internal Medicine

VOLUME 58

SEPTEMBER 1936

NUMBER 3

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## A CLINICAL SURVEY OF ONE HUNDRED AND EIGHT CONSECUTIVE CASES OF DIABETIC COMA

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Diabetic coma was first reported in the literature as a separate entity in 1828, when it was described by Stosch, it was later (1854) described by von Dusch, of Germany, and Marsh, of Scotland. However it remained for Kussmaul, of Strassbourg, twenty years later, to give the classic picture, in which he described the characteristic breathing, the *grosse Athmung*, which today bears his name and remains as perhaps the most pathognomonic clinical sign.

Prior to the memorable discovery of insulin by Banting and his associates in 1921 and its successful commercial preparation one year later, diabetic coma presented one of the most hopeless catastrophes of modern medicine. Before 1922 few writers had the courage to review a series of cases of diabetic coma with its disheartening mortality, but with the advent of insulin the situation assumed a right-about-face, and a number of excellent surveys have appeared. Notable among these surveys were those reported by the following investigators: Joslin and his associates<sup>1</sup> (six reports from the clinic of the New England Deaconess Hospital, 276 instances of coma in 228 cases), Bowen and Hek-

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This survey was carried out under the direction and supervision of Dr. Russell M. Wilder and Dr. E. H. Rynearson.

Abridgment of a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

1 (a) Joslin, E. P., Root, H. F., and White, Priscilla. Diabetic Coma and Its Treatment, *M. Clin. North America* **8** 1873-1919 (May) 1925, (b) Diabetic Coma and Its Treatment, *ibid.* **10** 1281-1306 (March) 1927. (c) Joslin, E. P., Root, H. F., White, Priscilla, Curtis, W. S., and Adams, H. D. Diabetic Coma, *ibid.* **13** 11-40 (July) 1929. (d) Joslin, E. P., Root, H. F., White, Priscilla, Jordan, W. R., and Hunt, Hazel M. Diabetic Coma, *ibid.* **15** 829-868 (Jan.) 1932. (e) Joslin, E. P., Root, H. F., White, Priscilla, Marble, Alexander, and Hunt, Hazel M. Diabetic Coma, *ibid.* **16** 793-827 (Jan.) 1933. (f) Marble, Alexander, Root, H. F., and White, Priscilla. Diabetic Coma, *New England J. Med.* **212** 288-297 (Feb. 14) 1935.

mian<sup>2</sup> (81 instances of coma in 63 cases), Dunlop<sup>3</sup> (45 cases of coma), John<sup>4</sup> (71 cases of coma) and Bertiam<sup>5</sup> (186 cases of coma). There is considerable variation in the percentage of recovery in these series, this, I believe, depends largely on such factors as the severity of the infection and other complications which may attend or precipitate coma and the average age of the patients. Another important factor with regard to recovery is the distance that it is necessary for the patients to travel to reach the particular hospital or clinic, this determines the important factor of the time that elapses between the onset of coma and the institution of treatment. Bertram<sup>6</sup> collected the reports of a series of 1,007 cases of diabetic coma cited by 25 authors since the use of insulin was begun and found the average mortality to be 29.1 per cent.

The present report is of a series of 108 instances of diabetic coma in 99 patients. There were 3 deaths from uncomplicated coma (2.8 per cent), 9 deaths from complications after recovery from coma and 5 deaths from complications without recovery from coma. The 3 deaths from uncomplicated coma occurred within two, ten and fifteen hours, respectively, after the admission of the patient to the hospital. The total mortality was 15.7 per cent. This series comprises the consecutive patients with diabetic coma who were seen at the Mayo Clinic from October 1923, when the first patient with coma was treated with insulin to January 1934. It should be noted that a number of patients were moribund at the time of admission to the hospital. In 10 cases coma had been present for more than twelve hours before the patient was admitted to the hospital, and in 7 of these cases it terminated fatally.

#### INTERPRETATION OF COMA

In the interpretation of what constitutes coma I am cognizant that if this interpretation were to depend solely on clinical judgment, the factor of the personal equation would assume an all too important rôle. Classification of the clinical condition into a state which has been designated as precoma and a state of coma without strict regard for chemical determinations allows too much ground for variation in clinical judgment. I have therefore included as cases of diabetic coma all cases, except 3, in which the value for the carbon dioxide-combining power of the plasma was 25 volumes per cent or less at the first determination.

2 Bowen, B. D., and Hekman, Ivan. Diabetic Coma. A Report of Eighty-One Instances, *Ann Int Med* **3** 1104-1111 (May) 1930.

3 Dunlop, L. W. Some Aspects of Diabetic Coma and Arteriosclerosis. *M. J. Australia* **2** 533-540 (Oct. 31) 1931.

4 John, H. J. Diabetic Coma, *J. A. M. A.* **93** 425-430 (Aug. 10) 1929.

5 Bertram, F. Die Prognose des Coma diabeticum, *München med. Wchnschr.* **2** 1643-1646 (Oct.) 1932.

6 Bertram, Ferdinand. Pathogenese und Prognose des Coma diabeticum. *Ergebn. d. inn. Med. u. Kinderh.* **43** 258-365, 1932.

after the patient was admitted to the hospital or in which it subsequently fell below this figure in the early course of treatment or following an operation. The 3 exceptions include 1 case (case 69) in which the determination of the carbon dioxide-combining power of the blood plasma was inadvertently omitted on the day the patient was admitted to the hospital, but the patient unquestionably was in clinical coma as the value for sugar was 840 mg per hundred cubic centimeters of blood and that for the carbon dioxide-combining power of the plasma was 28 volumes per cent after twelve hours of treatment. In a second case (case 81) in which the patient was admitted to the hospital in an unconscious state the value for the carbon dioxide-combining power of the plasma was 28 volumes per cent after 155 units of insulin had been administered by the referring physician. In a third case (case 94) in which the patient was admitted to the hospital in a deeply unconscious state the value for the sugar was 500 mg per hundred cubic centimeters of blood and that for the carbon dioxide-combining power of the plasma was 28 volumes per cent.

The value of 20 volumes per cent for the carbon dioxide-combining power of the plasma has been adopted by some clinics as the dividing line between a state of precoma and a state of coma. The objection to this is that clinical coma occasionally is observed in cases in which the value for the carbon dioxide-combining power of the plasma exceeds 25 volumes per cent, as illustrated by the 3 exceptions which have been cited, and that whenever the alkali reserve of a diabetic patient is less than 25 volumes per cent only energetic or heroic measures will insure recovery. In the era before insulin was used death almost invariably resulted in such cases. In 6 of the 17 cases in which death occurred the value for the carbon dioxide-combining power of the plasma was more than 20 volumes per cent when the patient was admitted to the hospital. These cases would not have been included in this report had I accepted as instances of coma only those cases in which the value for the carbon dioxide-combining power of the plasma was 20 volumes per cent, and the total mortality, instead of being 15.7 per cent, would have been 14.9 per cent.

#### INCIDENCE OF COMA AMONG DIABETIC PATIENTS

During 1931, 1932 and 1933 approximately 1,800 diabetic patients registered at the Mayo Clinic. Coma was present in 28 of these patients, an incidence of only 1.6 per cent. I feel certain that this is a low incidence of coma and probably is attributable to the fact that only 56 per cent of the patients who were in a state of coma when they arrived at the clinic were from Minnesota. The distance between the clinic and the homes of the majority of the diabetic patients who were under supervision here was usually too great to be undertaken in such an emergency. In a number of cases the diabetic patient who was in

a state of coma when he arrived at the clinic was on his way to Rochester for treatment when coma developed as a result of dietary indiscretion and omission of insulin on the train several hours before the patient's arrival at the clinic. Joslin<sup>1</sup> reported that the incidence of coma among all diabetic patients who were admitted to the hospital was 2.8 per cent, while John<sup>4</sup> reported an incidence of 4 per cent. The recent report by Solomon and Aring<sup>7</sup> of the incidence of diabetic coma among patients who were admitted to a general hospital is interesting. There were 37,438 admissions at the Boston City Hospital in 1933, and 1,167 or 3 per cent, of these patients were admitted in a comatose state. The dwindling incidence of diabetic coma is emphasized by the fact that of the 1,167 patients who were in coma, only 20, or 1.7 per cent, had diabetic coma.

TABLE 1—*Data on the Chronological and Seasonal Distribution of Diabetic Coma*

Year	Cases	Year	Cases
1922 (3 months)	3	1928	10
1923	19	1929	5
1924	12	1930	5
1925	5	1931	10
1926	7	1932	8
1927	14	1933	10
1922 to 1934			108

Month	Cases	Season	Cases	Month	Cases	Season	Cases
January	13	Winter	25	July	12	Summer	34
February	4			August	16		
March	8			September	6		
April	7	Spring	23	October	10	Autumn	26
May	10			November	12		
June	6			December	4		
1922 to 1934					108		108

*Chronological Distribution*—Table 1 illustrates the yearly and seasonal incidence in the 108 cases of diabetic coma. As will be seen, coma occurred more frequently in August than in any other month. August was also the leading offender in Joslin's series<sup>10</sup>. A larger number of patients were seen in the summer (June, July and August) than during any other season. This possibly may be explained by dietary infractions in the summer, plus the interruption of the diabetic regimen by a vacation. A higher incidence of coma during the winter, when infections of the upper portion of the respiratory tract are numerous, was the expectation, but there were fewer instances of coma in December and February than in any other months.

*Distribution According to Age and Sex*—Recent observations and impressions that diabetes is more prevalent among females than males, contrary to earlier reports, is corroborated in this series (fig. 1). Atten-

<sup>7</sup> Solomon, Philip, and Aring, C. D. The Causes of Coma in Patients Entering a General Hospital. *Am J M Sc* 188:805-811 (Dec.) 1934.

tion has been called also to the fact that the predilection for the female is greater among elderly patients and that diabetes is of a more severe grade among elderly women than it is among men of corresponding age<sup>8</sup> In the 37 cases of coma in which the patients were over 40 years of age, 26, or 70 per cent, of the patients were women

The average age of the entire group of patients was 31.2 years. The youngest patient was 3 years and the oldest one 74 years of age respectively. Both of these patients recovered. I have been unable to find an instance of recovery from diabetic coma cited in the literature in

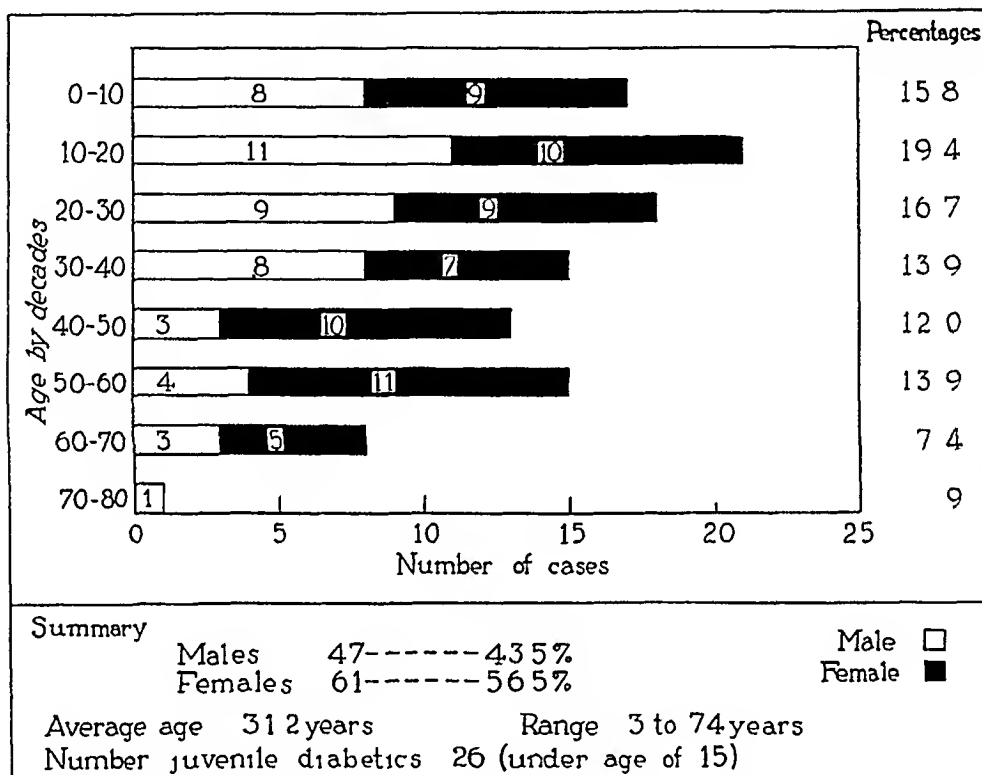


Fig 1—Distribution of the patients by age and sex. The distribution according to sex during the first four decades was practically equal, while females predominated among the patients over 40.

which the patient was as advanced in years as was the latter patient. The following is a brief résumé of the clinical history of this patient (case 96).

A man aged 74 years was admitted to the hospital in a stupor. The value for sugar was 469 mg per hundred cubic centimeters of blood, and that for the carbon dioxide-combining power of the plasma was 17 volumes per cent. He previously had not been aware of the existence of diabetes. His condition was complicated by myocardial degeneration, coronary sclerosis and auricular fibrillation. Recent

8 Joslin, E. P., Dublin, L. I., and Marks, H. H. Studies in Diabetes Mellitus. I. Characteristics and Trends of Diabetes Mortality Throughout the World. *Am J M Sc* **186**: 753-773 (Dec.) 1933.

correspondence revealed that now, at the age of 76, his health is good. He has gained 55 pounds (24.9 Kg) in weight and has not experienced any subsequent coma, despite the fact that he has undergone thyroidectomy in the interim.

The incidence of coma by decades is shown in figure 1, the highest incidence being in the second decade. Twenty-six patients (32 attacks of coma) were children who were less than 15 years of age. The mortality in the first four decades of life was 4 per cent (3 deaths among 71 patients with coma), and in the next four decades it was 40 per cent (14 deaths among 37 patients with coma).

#### DURATION OF DIABETES BEFORE THE ONSET OF COMA

The onset of diabetes was calculated from two angles: first, from the onset of symptoms, and, second, from the first detection of glycosuria. The average duration of diabetic symptoms before the onset of coma was twenty-six and one-half months, while the average time from the first discovery of glycosuria to the appearance of coma was twenty-three and one-half months. The average patient, therefore, had had diabetes for approximately three months before a diagnosis was made. In 1 case coma developed after the disease was known to have been present for ten years. On the reverse side of the ledger, 13 patients who were admitted in a comatose state had not had any previous knowledge of the presence of diabetes. In 51 per cent of the cases coma had developed within the first year of the disease. The rapidity with which coma may strike without any prodromal symptoms is most alarming. Particularly is this true of diabetic children, in whom the acid-base equilibrium may be upset by an insignificant dietary infraction or infection. It has been the experience in this clinic that the young diabetic patient, the elderly woman and the patient whose disease is of short duration are most frequently subject to coma.

#### PRECIPITATING FACTORS OF DIABETIC COMA

An interesting phase of this survey is the study of the precipitating factor in the individual case. In the great majority of cases coma can be ascribed to dietary indiscretion, omission of insulin or infection (table 2).

Dietary infractions and omission of insulin have been considered together because these factors frequently are joint perpetrators in precipitating coma. It is also true that most of the 17 cases listed in the group in which no precipitating factor was recorded rightfully belong in group 1. If these two groups are combined, it will be found that in 58, or 53.7 per cent, of all cases coma was the result of the failure of the patient or of the parents of the child to appreciate properly the importance of diet and the administration of insulin. The most striking

example of flagrant disregard for the diabetic routine occurred in case 78. This man, aged 53, was known to have had diabetes for five years. Coma was precipitated by an alcoholic debauch which lasted for three days. During that time little food other than alcohol was consumed and the administration of insulin was omitted entirely. Another patient (case 16) abandoned the use of insulin for chiropractic adjustments. Thus, it will be seen that ignorance and folly remain the worst enemies of the diabetic patient. However, 16 of the patients could not be held responsible for the coma, as the diagnosis of diabetes had been made only a few days prior to, and in some cases, during the coma.

The significance of infection in precipitating diabetic coma is well known. As Joslin has tersely expressed it "the diabetic is running in crowded traffic when in the midst of an infection." Infection was the

TABLE 2—*Data on the Precipitating Factors in Cases of Diabetic Coma*

Group		Cases	Percentage *
1	Dietary infractions and omission of insulin	40	37
	No therapy prior to coma	16	
	Dietary indiscretions and insufficient insulin	24	
2	Infection	32	30
	Respiratory infections	19	
	Pylonephritis	2	
	Gastro enteritis (?)	2	
	Appendicitis, cholecystitis, pancreatitis, septicemia, erysipelas, cellulitis and adenitis, rheumatic fever, measles and dengue fever (1 each)	9	
3	Operation (at clinic or elsewhere)	5	5
	Extraction of abscessed teeth	2	
	Cholecystectomy	1	
	Perineorrhaphy	1	
	Biopsy of lymph node (Hodgkin's disease)	1	
4	Miscellaneous and doubtful factors	13	11
	Exophthalmic goiter	6	
5	No recorded factor (cases probably belong to group 1)	18	17
	Total	108	100

\* Figures are approximate

precipitating factor in 32 cases. Predominant are the respiratory diseases, which accounted for more than half the attacks of coma attributable to infection as a precipitating factor. The respiratory diseases varied in degree from acute coryza to pneumonia and postpneumonic abscess. The common cold, with its sequelae was the offending factor in 7 cases. Pneumonia and influenza were held accountable in 9 cases. Among the other infections listed as causative factors in this series were streptococcic pharyngitis, erysipelas, cellulitis with suppurative adenitis, staphylococcic septicemia, active bilateral pulmonary tuberculosis, acute rheumatic fever, measles, pancreatitis, cholecystitis, appendicitis, dengue fever and gastro-enteritis (?).

In 5 cases the attacks of coma followed a surgical operation. The fact that a minor as well as a major surgical procedure may precipitate coma is well emphasized by the fact that the extraction elsewhere of



abscessed teeth was sufficient in 2 cases to precipitate coma. In a third case (case 92) in a woman aged 66, who previously had been debilitated by an old cerebral hemorrhage, the mere excision of a cervical lymph node for biopsy in Hodgkin's disease was sufficient to produce a change from diabetic balance on the day of operation to profound coma on the succeeding day. The value for sugar reached 560 mg per hundred cubic centimeters of blood, and the carbon dioxide-combining power of the plasma was 6 volumes per cent. In 1 case (case 65) the attack of coma followed simple perineorrhaphy complicated by post-operative pneumonia. Another case (case 80) in which the attack of coma was attributable to operation represents one of the few cases of insulin allergy noted at the clinic and will be considered later.

On the other hand, it is not unsafe to operate even in the presence of severe acidosis, provided the latter is combated energetically. In 9 cases in the present series a major operation was performed after the patient had recovered from the coma and before his dismissal from the hospital. Twelve minor operations, such as drainage of an empyema or tonsillectomy, also were performed in this group of cases.

Hyperthyroidism was among the miscellaneous group of factors which precipitated coma. The association of hyperthyroidism and diabetes is not uncommon, but sometimes it is a difficult task to ascertain which antedated or precipitated the other and which should be branded as the prime etiologic factor in the individual case. In the great majority of cases in which the patient was suffering from both diabetes and primary hyperthyroidism Wilder<sup>9</sup> and Joslin<sup>10</sup> have found hyperthyroidism to be the antedating disease.

In 6 of the present series of cases of coma hyperthyroidism was of such severity that I feel justified in classifying it as the factor which precipitated the coma. The basal metabolic rates of the patients ranged from +34 to +72. The highest reading was obtained in a patient (case 18) 69 years of age. A second attack of coma developed as a result of a preoperative thyroid crisis while the patient was in the hospital. She previously had experienced coma a short while before she was brought to the hospital. Here is an example of an elderly patient who suffered from three attacks of coma within the space of a few months, all of which were attributable to severe hyperthyroidism. After thyroidectomy there was no further difficulty, and she had no subsequent attacks of coma. The patient finally succumbed to heat prostration at the age of 80. The other 5 patients who were subjected

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9 Wilder, R. M. Hyperthyroidism, Myxedema and Diabetes, *Arch. Int. Med.* **38** 736-760 (Dec.) 1926.

10 Joslin, E. P. *The Treatment of Diabetes Mellitus*, ed. 4, Philadelphia, Lea & Febiger, 1928, p. 881.

to thyroidectomy following recovery from coma likewise had an uneventful convalescence, and they report no subsequent coma

Labbé<sup>11</sup> seems to have been the first to note the striking effect of the administration of iodine on the intensity of diabetes associated with exophthalmic goiter Wilder and Boothby<sup>12</sup> stressed the importance of the administration of iodine, intravenously if necessary with insulin in the treatment of coma associated with hyperthyroidism, if a successful outcome is to be expected

Among the other miscellaneous precipitating causes of diabetic coma in this series were coronary occlusion, intestinal obstruction from carcinoma of the sigmoid flexure the crisis of pernicious anemia abdominal trauma (?), emotional upset (?), hemochromatosis and acute yellow atrophy of the liver The last three require some comment

That hyperglycemia may result from an emotional crisis is established, but it seems difficult to conceive of a crisis of such extraordinary intensity as to precipitate coma However, this apparently is what happened in case 26, in which diabetes previously had been well controlled Coma developed (the value for the sugar was 420 mg per hundred cubic centimeters of blood and that for the carbon dioxide-combining power of the plasma was 11 volumes per cent) soon after the patient had learned of the accidental death of her son In this connection the interesting case reported by von Noorden<sup>13</sup> comes to mind, that of a bank director who apparently was in good health but who returned home after a stormy session and soon after dinner was found in coma by his valet

In the case in which coma was attributed to hemochromatosis, the coma is explained by the development of an unusual resistance to insulin This case has been reported elsewhere by Allan and Constan<sup>14</sup> The clinical history is as follows

CASE 63—A man aged 58 had suffered from diabetes secondary to hemochromatosis for seven months The diagnosis was established by biopsy of the skin and later was proved at necropsy On admission to the hospital the patient showed marked pigmentation of the skin, hepatic enlargement which extended 8 cm below the right costal margin, ascites and dependent edema Laboratory studies confirmed the presence of hepatic damage For seventy-four days the intensity of the diabetes varied considerably The value for the sugar ranged from 106 to 573 mg per hundred cubic centimeters of blood The patient finally lapsed into coma Despite the administration of huge doses of insulin, as much as 800 units

11 Labbé, Marcel Diabète et goitre exophtalmique *Ann de med* 7 95-103 1920

12 Wilder, R M, and Boothby, W M Metabolism Studies in Exophthalmic Goiter Complicated by Diabetes, *J Clin Investigation* 1 590 (Aug) 1925

13 von Noorden, quoted by John<sup>4</sup>

14 Allan, F N, and Constan, G R Insulin Resistance in a Case of Bronze Diabetes, *M Clin North America* 12 1677-1687 (May) 1929

being given in a single day, mostly intravenously, the value for the blood sugar was barely altered. The immediate cause of death was infected ascites which produced low grade peritonitis.

The following patient presented a somewhat similar problem.

CASE 84—A woman aged 33 was admitted to the hospital in profound coma which had been present for twenty-four hours. The value for the sugar was 320 mg per hundred cubic centimeters of blood, and that for the carbon dioxide-combining power of the plasma was 18 volumes per cent. The patient had been aware of the diabetes for only two days preceding the attack of coma. In all probability this represents a case of acute fulminating diabetes in which the inter-relationship between the pancreas and the liver was suddenly and violently disturbed. The patient was deeply jaundiced, and the amount of bilirubin in the serum was greatly increased. There was acute tenderness over the entire right upper quadrant of the abdomen. The test for hepatic function showed dye retention of grade 4. The urine showed positive results for tyrosine, and there was 75 mg of arsenic in 1,200 cc of urine. Contrary to the experience in the case of hemochromatosis, the recovery from coma was prompt after the administration of 190 units of insulin, but toxic nephrosis ensued. The value for urea gradually increased from 63 to 222 mg per hundred cubic centimeters of blood, and death occurred eighteen days after the patient was admitted to the hospital. Necropsy substantiated the diagnosis of acute yellow atrophy and toxic nephrosis and revealed atrophy and a definite decrease in the number of islands of Langerhans.

The recital of these unusual cases, however, should not divert emphasis from the usual triad of precipitating influences in diabetic coma, namely, dietary indiscretion, omission of insulin and infection, which in this series accounted for 90 or 83 per cent, of the 108 cases.

#### CLINICAL CONSIDERATIONS

Kussmaul breathing, nausea and vomiting, drowsiness or coma, hyperglycemia, ketonemia, glycosuria and ketonuria are the cardinal symptoms and signs of diabetic coma. Later, nausea and vomiting will be considered together with abdominal pain and leukocytosis and attention will be directed to the confusing similarity which may exist in cases of uncomplicated coma and acute surgical disease of the abdomen.

*Kussmaul Breathing*—This is perhaps the most significant clinical finding of impending or present coma, although it is not invariably present. Kussmaul respirations were recorded in 82.5 per cent of the cases in this series. In some cases ketonemia apparently had not reached the stage in which the accessory mechanism of pulmonary hyperventilation as a means of eliminating carbonic acid is called into play. Occasionally hyperpnea may disappear when the patient is exhausted after it has been present at the onset. This may be interpreted as due to toxic depression of the respiratory center in which the normal response to the stimulation of a lowered alkali content of the blood fails.

*Coma* —Coma in the sense of complete unconsciousness was present in 32 cases, stupor, in 32 cases, and drowsiness or marked lethargy, in 41 cases. In 2 cases a normal mental response was present, but these patients lapsed into unconsciousness after they were admitted to the hospital. The historian failed to mention the mental state in 1 case. Death occurred in 7 of the 10 cases in which coma was known to have been present for more than twelve hours before the patient was admitted to the hospital. There seems to be little correlation between the degree of unconsciousness of the patient and the degree of chemical change in the blood. The degree of unconsciousness depends less on the amount of sugar in the blood or the degree of the depression of the alkali reserve than it does on such factors as the presence of infection and the age of the patient. The surprising lack of correlation between the degree of clinical coma and the laboratory data will be considered later. It has been observed that patients between the ages of 12 and 45 years are much more likely to tolerate a decrease in the carbon dioxide-combining power of the plasma without losing consciousness than are very young or very old patients. Infection also predisposes to a lower threshold of consciousness.

*The Circulation in Coma* —Studies of the pulse and blood pressure in these cases of coma simply substantiated the observations of many investigators that a patient who has diabetic coma is essentially in shock and that the same remedial measures must often be employed for the two conditions. In 39 cases the pulse rate exceeded 120 beats per minute at the time the patient was admitted to the hospital, the 2 highest rates occurred in cases in which coma was associated with hyperthyroidism. Two patients were pulseless, and auricular fibrillation was present in 3 cases. The value for the systolic blood pressure was less than 90 mm of mercury in a surprisingly small number of the adult patients. In 32 cases there was some suggestion of cardiac abnormality, which was indicated either in the electrocardiogram or with the stethoscope, but a large number of these irregularities undoubtedly were functional in origin. Circulatory collapse was definitely responsible for the death of 1 patient who probably would have survived uncomplicated coma.

*Tension of the Eyeball and Examination of the Ocular Fundus* —The data in these cases unfortunately are inadequate on the subject of the tension of the eyeball. Purves-Stewart<sup>15</sup> expressed the opinion that the lowered ocular tension in cases of diabetic coma is only another manifestation of the general dehydration of the tissues. Joslin<sup>14</sup> found

15 Purves-Stewart, James. *The Diagnosis of Nervous Diseases*, ed 7, London, Edward Arnold & Co, 1931, p 118.

ocular hypotonia on palpation in 58 per cent of 38 children with diabetic coma. The sign does not signify as poor a prognosis as it formerly was believed to indicate.

The ocular fundus was examined almost as a routine in these cases. It was normal in 78 per cent of the cases, and in only 14 per cent could the changes be ascribed to diabetes. Lipaemia retinalis was present in 7 cases. These results agree roughly with those reported in the recent study by Wagener, Day and Wilder,<sup>16</sup> in which there was an incidence of 17.7 per cent of fundal lesions among 1,052 diabetic patients. Cataract was present in only 1 case in this series.

#### DIABETIC ACIDOSIS VERSUS ACUTE SURGICAL DISEASE OF THE ABDOMEN

I have been particularly interested in the frequency with which severe acidosis may mimic acute surgical disease of the abdomen. The diabetic patient who has severe acidosis with abdominal pain, vomiting and abdominal tenderness presents one of the most perplexing problems confronted by either the internist or the surgeon, one which requires the most careful evaluation of clinical and laboratory data. Particularly does this apply to children. The frequency with which this situation arises is more prevalent than has been suspected, as the accompanying statistics will show. To operate in the presence of uncomplicated diabetes is to expose a seriously ill patient to an unnecessary hazard yet to disregard this triad of symptoms simply because the patient has acidosis is to invite disaster occasionally by neglecting a gangrenous appendix, which may be causing the acidosis. The quandary in which the physician finds himself is not alleviated by the presence of leukocytosis, as will be shown.

The difficulty in making a differential diagnosis in these cases is well illustrated by the following case which previously has been reported in detail.<sup>17</sup>

CASE 41.—A girl aged 9 years had been known to have diabetes for seventeen months. Prior to two weeks before her admission to the hospital the disease had been well controlled. Then an acute colicky abdominal pain had developed with anorexia and nausea. The pain had subsided in two days but had returned a few days later, when it had been associated with vomiting and tenderness over the lower half of the abdomen, especially on the right side, so that the physician had suspected appendicitis and had referred the child to the clinic. On her arrival here she was weak, stuporous and hyperpneic. Definite tenderness and rigidity of the abdomen were not elicited, although the examination was admittedly unsat-

16 Wagener, H. P., Day, T. S., and Wilder, R. M. Retinitis in Diabetes. *New England J. Med.* **211**: 1131-1137 (Dec. 20) 1934.

17 Allan, F. N. Diabetic Acidosis and Leukocytosis, *Am. J. M. Sc.* **174**: 506-510 (Oct.) 1927.

isfactory on account of the hyperpnea. The value for sugar was 338 mg per hundred cubic centimeters of blood and that for the carbon dioxide-combining power of the plasma was 12 volumes per cent. The temperature was normal. A roentgenogram of the thorax did not reveal any abnormality of the lungs. The number of leukocytes ranged from 59,100 to 66,400 per cubic millimeter of blood, 90 per cent of these were polymorphonuclear neutrophils.

The next morning, after energetic treatment had been employed to combat the acidosis, the patient seemed almost entirely normal. The value for the carbon dioxide-combining power of the plasma was then 30 volumes per cent and that for the leukocytes had fallen to 20,200 per cubic millimeter of blood. The next day it had decreased to 16,000 per cubic millimeter of blood, and a day later it was normal. Recovery was uneventful, but it was thought advisable to perform an appendectomy two weeks later. The pathologic report was "chronic catarrhal appendicitis, grade 1" (on the basis of 4). Correspondence has revealed that no similar attacks of coma have occurred in this case in the succeeding nine years.

This case presented the problem which I have just mentioned. The child obviously had acidosis, but whether or not appendicitis was the precipitating factor in initiating the acidosis was the pressing question. The value for the leukocytes was so great that it was felt that appendicitis, if present, probably had progressed to peritonitis. Largely for this reason, but also on account of the great risk entailed by operation, it was considered best to combat the acidosis vigorously and to await developments. It seems more plausible to ascribe the extreme leukocytosis in this case to the acidosis alone than it does to assume that such a negligible grade of appendicitis was the basis for such severe acidosis.

Another child, aged 12 years (case 35), was suffering from such acute abdominal pain at the time of her admission to the hospital that volvulus was suspected for a number of hours, but the prompt response to treatment with insulin proved the abdominal symptoms to be secondary to acidosis.

While these and other cases show that acidosis alone may often mimic acute surgical disease of the abdomen, there have been others in which acute abdominal disease precipitated the acidosis. The cases reported by Smith<sup>18</sup> are interesting in this respect. A boy, whose story is almost duplicated by the case just detailed, except that the acidosis was not so severe and the tenderness and rigidity of the rectus muscles was more marked, was treated recently at the clinic. The leukocytes numbered 25,000 per cubic millimeter of blood. Operation was performed, and a ruptured appendix with peritonitis was revealed. Although the child had a stormy convalescence, complicated by pertussis, which was present at the time of his admission to the hospital, he finally recovered.

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18 Smith, J. H. Intra-Abdominal Inflammation in Relation to Diabetic Acidosis with Leukocytosis, *J. A. M. A.* 92:308-309 (Jan. 26) 1929.

Table 3 summarizes the data in this division of the study. In a number of cases the presence or absence of abdominal symptoms was not specifically mentioned. It is for this reason that two tables of percentages are presented, the first is based on the entire series and the second on the number of cases in which these facts were accurately recorded.

Definite abdominal pain was present in 34 of the 108 cases, or in 41 per cent of the 82 cases in which the presence or absence of this symptom was recorded. In 5 of the 34 cases the abdominal pain could probably be ascribed to the precipitating factor. Empyema of the gall-bladder, intestinal obstruction, appendicitis, bilateral pyelonephritis or ruptured esophageal varices secondary to syphilitic hepatosplenomegaly

TABLE 3—*Data on the Abdominal Symptoms in Cases of Diabetic Coma*

Symptoms	Cases		Percentage*	
	Symptoms Present	Presence or Absence of Symptoms Was Recorded	Based on 108 Cases	Based on Cases in Which Presence or Absence of Symptoms Was Recorded
Abdominal pain	34	82	32	41
From acidosis alone	29			
From other causes	5			
Nausea and vomiting	57	85	53	68
From acidosis alone	40			
From other causes	17			
Leukocytosis, more than 12,000 per cu. mm.	38	69	35	55
From acidosis alone	25			
From other causes	13			
Abdominal pain and vomiting	25	82	23	31
Abdominal pain, vomiting and leukocytosis of more than 12,000 per cu. mm.	16	69	15	23

Figures are approximate.

were the respective precipitating factors in these 5 cases. Therefore, in 29 cases the abdominal pain could not be ascribed to anything save coma alone. The subsequent course in each case substantiated this diagnosis.

Nausea and vomiting were present in 57, or 67 per cent, of the 85 cases in which the presence or absence of these symptoms was recorded.

The presence of leukocytosis in cases of uncomplicated coma previously has been noted by a number of careful observers.<sup>19</sup> Dehydration has been advanced as a possible cause for it in cases of uncomplicated coma, but the relative constancy of the value for hemoglobin and of the number of erythrocytes does not substantiate this view. More than 12,000 leukocytes per cubic millimeter of blood were present in 38, or

<sup>19</sup> Joslin<sup>1b</sup> Allan<sup>17</sup> Smith<sup>18</sup>

55 per cent, of the 69 cases in which a blood count was made at the time the patient was admitted to the hospital. However, in 13 cases, in addition to acidosis, there was some coexistent infection which may have accounted for the increase in the number of leukocytes. Therefore, in 25, or 36 per cent, of the 69 cases in which blood counts were made leukocytosis could be explained by acidosis alone.

While other abdominal emergencies may precipitate diabetic coma, appendicitis must be excluded in the great majority of cases before one can ascribe abdominal symptoms to acidosis alone. Each condition may resemble the other in its early symptoms. Coma is often consequent on appendicitis, either before or after operation. In determining the question of whether or not the abdominal symptoms are dependent on acidosis alone or appendicitis plus a secondary acidosis, only the close cooperation of clinicians and surgeons who have had extensive experience with diabetic patients can assure a high average of successful decisions, and even here errors on both sides of the ledger will inevitably occur. The mental status of the patient, which is dependent on the degree of acidosis present, is often a deciding factor, as the decision may hinge on the degree of cooperation afforded by the patient while the abdomen is being examined.

Just how frequently this perplexing situation arises may be appreciated from the number of these patients who had abdominal pain plus nausea and vomiting and a leukocyte count in excess of 12,000 per cubic millimeter. There were 16 such patients in this series. Many of them came to the clinic with a diagnosis of appendicitis, and in only 5 cases could a coexisting disease which would account for the symptoms be diagnosed. There was an additional group of 9 cases in which abdominal pain, nausea and vomiting were present but in which no leukocyte count was made at the time the patient was admitted to the hospital, thereby making a total of 25 cases in which there was a potential possibility that acute surgical disease of the abdomen was the underlying cause of the coma. However, it is not probable that this last named group of 9 cases caused the clinician any considerable worry from a surgical standpoint, for had this been true, a leukocyte count would have been made. Only 3 of the 25 patients required abdominal exploration—1 for empyema of the gallbladder, 1 for appendicitis and 1 for colostomy for carcinomatous obstruction of the sigmoid flexure. This emphasizes the fact that error, when it occurs, is more likely to be on the side of unnecessary operation, as Smith<sup>18</sup> has said, "anti-ketosis must rank with asepsis in the surgical conscience."

Various hypotheses have been proposed to explain the mechanism of the production of abdominal symptoms in cases of diabetic acidosis. Foremost among them is gastric distention, which undoubtedly often exists. However, it would be enlightening to know how great a part



episodes of subacute pancreatitis play in the cases in which diabetic acidosis simulates acute surgical disease of the abdomen

#### DISCREPANCIES BETWEEN CLINICAL AND LABORATORY DATA

*Blood Sugar*—Lawrence<sup>20</sup> has reported the highest concentration of sugar in the blood with which I am familiar—2,060 mg per hundred cubic centimeters. Aigy<sup>21</sup> has reported the case of a diabetic Negro who went on a sweetened lemonade debauch resulting in rapidly fatal coma with the value for the blood sugar 1,710 mg per hundred cubic centimeters. To Dillon and Dyer<sup>22</sup> goes credit for reporting the

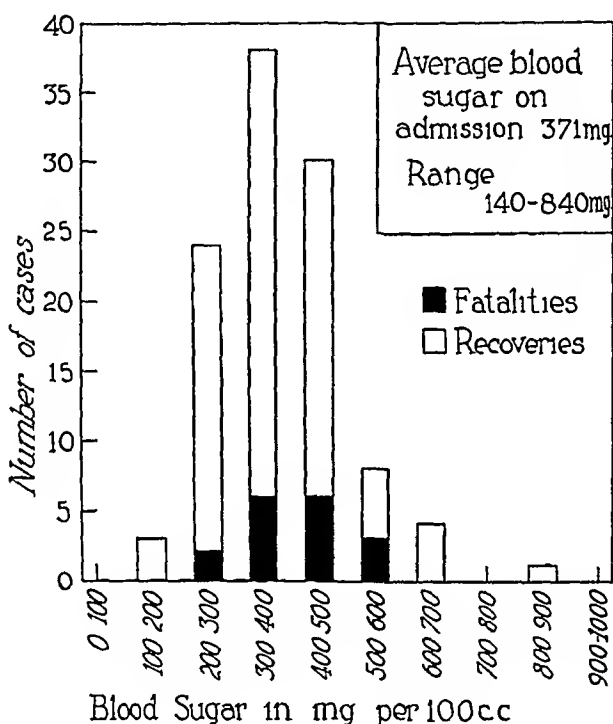


Fig 2—Distribution of patients according to the degree of hyperglycemia at the time they were admitted to the hospital. A number of patients who revealed low values for blood sugar had received large doses of insulin prior to the making of the determination.

highest value for the blood sugar in a case of nonfatal coma (1,850 mg per hundred cubic centimeters). This series of cases is conspicuous for the absence of exceptionally high values for blood sugar. Figure 2

20 Lawrence, R. D. Extreme Hyperglycemia in Diabetic Coma, *Brit. M. J.* **1** 377 (March 3) 1934.

21 Aigy, W. P. An Unusual Case of Hyperglycemia (One and Seventy-One Hundredths Per Cent) with Coma, Associated with an Absence of Acetone in the Urine. Report of a Case, *Boston M. & S. J.* **193** 1236-1237 (Dec 31) 1925.

22 Dillon, E. S. and Dyer, W. W. Diabetic Coma with Extreme Hyperglycemia, *Am. J. M. Sc.* **190** 683-686 (Nov) 1935.

shows the average value to be 371 mg per hundred cubic centimeters of blood in this survey. The range was from 140 to 840 mg. At least 15 of these patients had received insulin prior to the making of these determinations. Joslin<sup>12</sup> has reported 1 case of coma in which the value for sugar was only 130 mg per hundred cubic centimeters of blood.

I have been particularly impressed with the extreme variability of the values for the blood sugar and the carbon dioxide-combining power of the plasma in cases in which there was deep coma. There seems to be surprisingly little correlation between the laboratory and the clinical data. One patient becomes comatose when the value for sugar is less than 300 mg per hundred cubic centimeters of blood, while another tolerates hyperglycemia in which the value for sugar is 600 mg per hundred cubic centimeters of blood and only becomes drowsy. Bruger<sup>23</sup> recently reported a remarkable case in which the patient tolerated 1,500 mg of sugar per hundred cubic centimeters of blood without the development of coma. Obviously there must be factors which would explain this situation satisfactorily. In an attempt to arrive at the answer to this problem the patients in this series of cases have been classified into three groups. This classification was based on the mental state of the patient at the time of his admission to the hospital. Under the heading drowsy are included those patients who were listless and lethargic and showed no interest in their condition or surroundings, under the term stuporous are grouped those who could be aroused from unconsciousness only by such strong stimuli as shaking or shouting and under comatose are classified those whose degree of unconsciousness was so deep that they could not be aroused by any ordinary stimulus.

The results of the laboratory studies of these groups of patients appear in table 4. It will be observed that there is a difference of less than 100 mg between the average value for blood sugar of the group classified as drowsy and that of the group classified as comatose. In 8 cases in which the mental state of the patient was designated as drowsy the average value for blood sugar exceeded that of the comatose patients, and conversely, in 10 cases in which the patients were comatose the average value for blood sugar was less than that of the group of drowsy patients.

Two factors seem responsible for this paradoxical situation, namely (1) the presence or absence of coexisting infection and (2) the age of the patient. From a study of the group of comatose patients in whom the value for blood sugar was comparatively low it was found that,

23 Bruger, Maurice. Diabetes Mellitus and Hyperthyroidism. Report of a Case with a Fasting Blood Sugar of Fifteen Hundred Milligrams per Hundred Cubic Centimeters in the Absence of Coma, *J A M A* **104** 2163-2164 (June 15) 1935.

almost without exception, the patients were more than 50 or less than 12 years of age, and in the few cases in which this was not true, coma was complicated by acute and overwhelming infection. Likewise, it was discovered that with only 2 exceptions all the drowsy patients who tolerated a concentration of blood sugar which was higher than that of the comatose patients were between the ages of 12 and 45 years and that little or no infection was present.

Of 95 patients who showed a value for sugar of less than 500 mg per hundred cubic centimeters of blood, 14 (15 per cent) died. Of 13 patients who showed a value for sugar of more than 500 mg per hundred cubic centimeters of blood, 3 (23 per cent) died. This difference in the mortality does not seem particularly impressive, and it does not seem that a high value for blood sugar per se is necessarily prejudicial to ultimate recovery from coma. It also was noted that in the 3 cases in which the patient died of uncomplicated coma the values for sugar were only 278, 432 and 519 mg, respectively, per hundred cubic centimeter of blood.

As the value for blood sugar frequently does not parallel the clinical condition of the patient, it obviously is not a reliable criterion on which to judge the severity of the diabetic coma in an individual case. A "laboratory cure" results not infrequently while the patient sinks rapidly, less often the reverse is true.

*Carbon Dioxide-Combining Power of the Plasma*—Two patients who at the time of admission to the hospital revealed a carbon dioxide-combining power of only 2 volumes per cent (2.2 and 2.5 volumes per cent, respectively) have been observed. Both patients recovered. Equally low values for this combining power of the plasma have been reported by other writers, but I have been unable to find mention of any case in the literature in which the value was lower than this.

The average value for the carbon dioxide-combining power of the plasma for the entire series was 16.8 volumes per cent (fig. 3). The relation of the carbon dioxide-combining power and the value for blood sugar to the mental state of the patient is recorded in table 4.

In general, unconsciousness is almost always present when the value for the carbon dioxide-combining power of the plasma is less than 12 volumes per cent, but the individual thresholds of consciousness vary greatly. Five patients who disclosed values of less than 12 volumes per cent were classified as only drowsy or stuporous, while 3 patients who showed a carbon dioxide-combining power of 28 volumes per cent were in profound coma. Again, 4 of these 5 patients who tolerated low values for the carbon dioxide-combining power of the plasma without becoming comatose were between 12 and 45 years of age, while con-

versely, the factors of infection and extremes of age explained the degree of unconsciousness in the cases in which the patient was comatose and the alkali reserve was not markedly reduced

While the value for the carbon dioxide-combining power of the plasma more nearly paralleled the clinical condition of the patient than

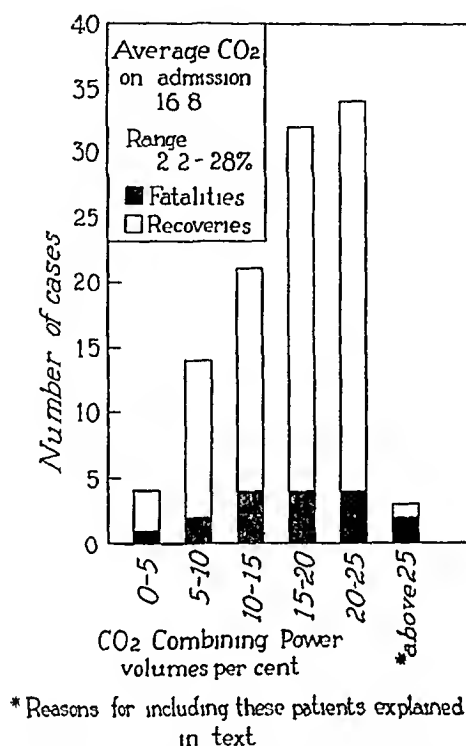


Fig 3—Distribution of patients according to the carbon dioxide-combining power of the plasma at the time they were admitted to the hospital

TABLE 4—*Correlation of Laboratory Data with Mental State in Cases of Diabetic Coma*

Mental Status	Number of Patients*	Blood Sugar, Mg per 100 Ce		Carbon Dioxide Combining Power of Plasma, Vol %	
		Average	Range	Average	Range
Drowsy	41	330†	188 to 571	21	11 to 25
Stuporous	32	363	140† to 652	17	8 to 24
Comatose	32	423§	222‡ to 840	12	2 to 28‡

\* The mental status of 3 patients was not classified

† In 8 patients in the "drowsy" group the average value for the blood sugar exceeded that of the cases in the "comatose" group

‡ Insulin was administered prior to the chemical examination which revealed this value

§ In 10 patients in the "comatose" group the average value for blood sugar was less than that in cases in the "drowsy" group

did the value for the blood sugar, there was no appreciable difference in the mortality in cases in which the value for the carbon dioxide-combining power of the plasma was more than 15 volumes per cent and that in cases in which it was less than 15 volumes per cent. Death occurred in 7 (18 per cent) of the 39 cases in which the value for the

carbon dioxide-combining power of the plasma was less than 15 volumes per cent, and in 10 (14 per cent) of the 69 cases in which it was between 15 and 25 volumes per cent

An analysis of the 18 cases in which the value for the carbon dioxide-combining power of the plasma was exceedingly low—10 volumes per cent or less—at the time the patient was admitted to the hospital reveals a most interesting observation (table 5). In this group there were only 3 deaths, or a mortality of 16.6 per cent. If this is compared with the mortality of 15.7 per cent for the entire series, it seems to indicate that the decrease of the alkali reserve of the plasma, once it has decreased to 25 volumes per cent, has little influence on the ultimate prognosis. This situation may perhaps be explained by the fact that there was a comparative absence of infection in these 18 cases (table 5). The presence or absence of infection complicating diabetic coma seems of greater consideration than do the values for blood sugar or the alkali reserve in determining the prognosis.

TABLE 5—*Results of Treatment in Cases of Diabetic Coma in Which Values for the Carbon Dioxide-Combining Power of the Plasma Did Not Exceed Ten Volumes Per Cent*

Carbon Dioxide Combining Power of Plasma, Vol %	Cases	Complications	Recovery	Death
2	2		2	
3	1			1
4	1	Streptococcal pharyngitis	1	
6	1		1	
7	1			1
8	4		4	
9	4	Exophthalmic goiter in 1 case	4	
10	4	Pneumonia in 1 case	3	1*
Total	18		15	3

\* This death occurred in the case in which pneumonia was a complication.

*Retention of Urea*—The number of cases in which there was an abnormal concentration of urea in the blood without previous evidence of organic renal disease preceding coma places this observation beyond the realm of coincidence. Moderate albuminuria, casts and a few erythrocytes were present in the urine in the majority of cases, but these seemed to be the expression of a pathologic physiology of a temporary nature, which apparently leaves little or no residuum after coma. In 54 cases in this series the value for the urea nitrogen of the blood was determined when the patient entered the hospital. In 27 cases, or exactly half of those for whom this value was determined, there was more than 35 mg of urea per hundred cubic centimeters of blood. The value for the urea exceeded 50 mg per hundred cubic centimeters of blood in 17 cases, and in 3 cases it was more than 100 mg. Coma in 2 of the latter 3 cases was uncomplicated by permanent

renal changes, both patients made a satisfactory recovery, while the third patient was the victim of severe cardiorenal decompensation

The retention of urea in cases of diabetic coma is not always transitory. Occasionally, in a case in which there has been no previous renal damage, the hyperglycemia and acidosis respond promptly to treatment, while the value for blood urea steadily increases as the result of anuria from renal block. Anuria is one of the most serious complications which may follow diabetic coma. It usually appears from twenty-four to forty-eight hours after the onset of coma and frequently after the coma appears to have been controlled. The exact cause of the anuria of diabetic coma is not adequately explained. The following factors have been suggested: (1) circulatory disturbance in the kidney accompanying a decrease of blood pressure and cardiac failure,<sup>24</sup> (2) dehydration of the blood plasma as a result of a lack of intake of fluid, previous polyuria and vomiting,<sup>25</sup> (3) increased endogenous nitrogen metabolism,<sup>26</sup> and (4) actual pathologic change in the renal parenchyma as a result of an excessive excretion of ketone acids and salts and other metabolites in the early stages of coma.<sup>27</sup>

The report of Fullerton, Lyall and Davidson<sup>24</sup> emphasized the gravity of the situation when an increase in the amount of blood urea accompanies coma. They reported 4 deaths in 6 cases of diabetic coma in which the values for urea exceeded 100 mg per hundred cubic centimeters of blood, and only 1 death in 13 cases in which the values for blood urea were less than this figure. In a recent report from the New England Deaconess Hospital anuria was apparently the cause of 4 of the 6 deaths in cases of diabetic coma and was a contributing factor to death in a fifth case.<sup>1f</sup>

Again, steadily increasing values for blood urea in a case in which there is no previous history of renal disease may be explained by the presence of toxic nephrosis which is secondary to overwhelming toxemia and independent of acidosis. This was true of case 84, in which successive determinations revealed 63, 88, 138, 174, 192 and finally 222 mg of urea per hundred cubic centimeters of blood as a result of arsenical (?) toxic nephrosis and acute yellow atrophy of the liver

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24 Fullerton, H. W., Lyall, A., and Davidson, L. S. P. The Treatment of Diabetic Uraemia with Hypertonic Glucose Solutions, *Lancet* **1** 558-560 (March 12) 1932

25 Bulger, H. A., and Peters, J. P. Concentration of the Blood and of the Urine in Diabetic Toxemia, *Arch. Int. Med.* **36** 857-873 (Dec.) 1925

26 Lyall, Alexander. On the Effect of Protein in the Diet of Patients Suffering from Diabetes Mellitus, *Quart. J. Med.* **20** 115-122 (Jan.) 1927

27 Snapper, I. Rôle of the Kidney in Non-Renal Disorders. I. Diabetic Coma Without Ketonuria, II. Coma, Non-Diabetic, with Glycosuria and Hyperglycemia, *Proc. Roy. Soc. Med. (Sect. Med.)* **21** 73-76 (Sept.) 1928

*Glycosuria and Ketonuria*—Tests for the presence of glycosuria and ketonuria have long been and continue to be among the most valuable and practical tests of diabetic acidosis for the physician to whom determinations of the chemical constituents of the blood are not readily available, but they are by no means infallible. It is well established that the presence of sugar in the urine does not prove the existence of diabetes, at the same time, the absence of acetonuria does not exclude acidosis. The clinician not infrequently is confronted with a patient who is in a comatose state as a result of cerebral hemorrhage and who reveals a moderately high degree of glycosuria and hyperglycemia, whereas, occasionally, a profoundly comatose patient who reveals excessive hyperglycemia will not show any glycosuria.

The highest value for sugar in the urine in this series of cases was 875 per cent, and it was noted in a case in which the diagnosis of coma was barely sustained by the clinical and laboratory examinations. In only 41 per cent of the cases in which the level of the urinary sugar was determined quantitatively at the time the patient was admitted to the hospital was the concentration as high as 3 per cent. As a yardstick of the severity of coma, quantitative analyses of the sugar in the urine are in no way reliable.

Ketonuria is almost always noted in cases of diabetic acidosis, but here again the exceptions prove the rule. John,<sup>4</sup> Lemann,<sup>28</sup> Starr and Fitz,<sup>29</sup> Coburn,<sup>30</sup> Argy,<sup>21</sup> Rudy and Levin,<sup>31</sup> Appel and Cooper<sup>32</sup> and others have reported cases of diabetic coma without ketonuria. There were 3 such cases in this series. In most of the reported cases of coma without ketonuria there was usually sufficient clinical or postmortem evidence of renal damage to explain this finding. However, in a considerable percentage of reported cases there was no evidence of coexisting renal changes. In 1 of the 3 cases in this series in which there was no ketonuria but a strong odor of acetone on the breath, coma was complicated by extensive bilateral pyelonephritis, which eventually caused death. Coburn<sup>30</sup> noted that in cases in which there was no ketonuria the patient remained semicomatose until the excretion of ketone acids

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28 Lemann, I I. Pitfalls in the Diagnosis of Diabetic Coma, *M Clin North America* **9** 959-969 (Jan) 1926

29 Starr, Paul, and Fitz, Reginald. The Excretion of Organic Acids in the Urine of Patients with Diabetes Mellitus, *Arch Int Med* **33** 97-108 (Jan) 1924

30 Coburn, A F. Diabetic Ketosis and Functional Renal Insufficiency, *Am J M Sc* **180** 178-192 (Aug) 1930

31 Rudy, Abraham, and Levin, C M. Unusual Case of Diabetic Acidosis Without Ketonuria or Ketonemia, *New York State J Med* **27** 1240-1243 (Nov 15) 1927

32 Appel, K E, and Cooper, D A. Diabetic Acidosis with Negative Ferric-Chloride Reaction in the Urine. Report of Five Cases, *Am J M Sc* **173** 201-220 (Feb) 1927

was resumed. In 3 cases in which an indwelling catheter was employed he noticed that the disappearance of acetone from the urine preceded anuria. Feinblatt<sup>33</sup> has reported an unusual case of fatal juvenile coma in which there was insignificant ketonuria, but large amounts of acetone were present in the spinal fluid. Insulin had no therapeutic effect. Also in the remarkable case described by Argy, in which the value for the blood sugar was one of the highest that has been reported, there was no ketonuria, but a large amount of acetone was present in the spinal fluid.

It is obvious that these patients have acidosis yet there is no ketonuria or ketonemia, so the ketone bodies cannot be indicted as the cause of acidosis in all cases of diabetic coma. Furthermore Stair and Fitz<sup>34</sup> have shown that in a certain proportion of cases of diabetes mellitus (14 of 114) the amount of undetermined organic acid excreted in the urine was much in excess of the total ketone acids—the reverse of what usually occurs—and that this acid may account for the total organic acids excreted in the cases in which there was no ketonuria. Himwich<sup>35</sup> has recently reported that the unknown organic acid, in addition to the ketone bodies, in the urine of dogs which had diabetic acidosis was lactic acid. It is in these cases that the administration of insulin is seemingly ineffective and the administration of alkalis is advised. Finally, Allen and Wishart<sup>35</sup> in a series of excellent experimental studies on acidosis in phlorhizinized dogs could not discover any parallelism between ketonuria, ketonemia and the amount of sodium bicarbonate in the plasma. They found that death may result with either a high or a low value for sodium bicarbonate in the plasma and with either a large or a small amount of ketone bodies in the blood.

#### OBSERVATIONS ON TREATMENT

*The Use of Insulin*—The timidity which characterized the use of insulin in the years immediately following its discovery is reflected in the fact that the average patient who was treated for diabetic coma at the clinic in 1923 received only 67 units of insulin in the first twenty-four hours after his admission to the hospital, while the average dose in 1931 was 148 units. No definite rules for determining the correct dose of insulin can be formulated, for each patient is truly an individual therapeutic problem. However, there were three factors which seemed of primary consideration in determining the total dose required in the

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33 Feinblatt, H. M. Report of a Fatal Case of Juvenile Diabetic Coma with Insignificant Ketonuria and with a Large Amount of Acetone in the Spinal Fluid, *Arch. Int. Med.* **34** 508-510 (Oct.) 1924.

34 Himwich, H. E. The Metabolism of Fever, with Special Reference to Diabetic Hyperpyrexia, *Bull. New York Acad. Med.* **10** 16-36 (Jan.) 1934.

35 Allen, F. M., and Wishart, Mary B. Experimental Studies in Diabetes V. Acidosis in Phlorizinized Dogs, *J. Metabolic Research* **4** 223-254, 1923.



first twenty-four hours after the patient's admission to the hospital, namely (1) the age of the patient, (2) the depth of the coma, as measured by the degree of unconsciousness (this is usually more dependent on the duration of coma before the institution of treatment than on the hyperglycemia or the depletion of the alkali reserve), and (3) the presence or absence of infection

The age factor is emphasized by the fact that the diabetic patients who were less than 15 years of age required an average of 59 units of insulin in contrast to the average dose of 111 units for adults in the first twenty-four hours after admission to the hospital. In a completely unconscious 7 year old child who showed a carbon dioxide-combining power of the plasma of only 9 volumes per cent, coma was relieved by the total amount of only 28 units of insulin. In another child, aged 11 years, who showed a carbon dioxide-combining power of the plasma of only 2 volumes per cent, coma was relieved by the administration of only 70 units of insulin. The average dose of insulin in the first twenty-four hours for the entire group of patients was found to be 97 units, but it must be remembered that a large number of these patients were treated between 1922 and 1925, and it is admitted in the light of present knowledge that they were given inadequate doses of insulin. The extremes of the doses of insulin administered in the first twenty-four hours varied from less than 10 units in an insulin-sensitive person, who fortunately was in a mild coma, to 500 units, which was required by an insulin-resistant patient. It subsequently was necessary to give the latter patient a total of 980 units, mostly intravenously, before the coma was finally relieved.

It has been our experience at the clinic that the degree of unconsciousness is a better criterion in determining the total amount of insulin required to relieve coma than is the value for blood sugar or that for the carbon dioxide-combining power of the plasma, although, of course, the laboratory and clinical data often parallel each other. The average dose of insulin administered in the first twenty-four hours to a totally unconscious patient was 170 units, for a similar condition since 1930 the average dose has been 253 units.

As a matter of comparison, it is interesting to find that in only 6 of the 13 cases in which the value for sugar exceeded 500 mg per hundred cubic centimeters of blood did the patient receive more insulin in the first twenty-four hours than the average amount for the entire series. Similarly, the amount of insulin required in the first twenty-four hours by the group in which the value for the carbon dioxide-combining power of the plasma was markedly decreased (10 volumes per cent or below) at the time the patient was admitted to the hospital reveals the same lack of correlation. It therefore seems that the degree of unconsciousness of the patient is a factor of greater importance in

determining the total amount of insulin required to relieve coma than the value for blood sugar or the depth of depletion of the alkali reserve. This has also been the experience of Bowen and Hekimian,<sup>2</sup> who said that "this requirement [the dosage of insulin in the first twenty-four hours] did not appear to have any direct relationship to the height of the blood sugar, the carbon dioxide-combining power, leukocytosis or blood urea nitrogen, although we usually expected a patient with extreme hyperglycemia to tolerate more insulin."

The duration of coma before the institution of treatment frequently determines the depth of unconsciousness of the patient at the time of his admission to the hospital. It is generally true that coma which has been present for more than twelve hours before treatment is begun is refractory to insulin,<sup>3</sup> and large doses are required before any appreciable improvement can be detected. This is illustrated by the case of a woman (case 81) who had been unconscious for more than twelve hours before her admission to the hospital. Although 275 units of insulin was administered, there was no improvement, and she died within two hours after her admission to the hospital. There were 10 patients in the series who had been unconscious for more than twelve hours before the institution of treatment. Of this group, only 3 survived, 6 died within from two to fifteen hours after admission to the hospital, while another recovered from coma but died later. Coma of long duration is always a grave prognostic sign. This factor must always be considered in evaluating the mortality in any series of cases of diabetic coma.

The fact that more insulin is required in a case in which coma is precipitated by an acute fulminating infection than is required in a case of uncomplicated coma in which the degree of hyperglycemia is the same is well established and requires no statistical elaboration.

The amount of insulin to be administered within the first twenty-four hours after the patient's admission to the hospital is thus determined by the age of the patient, the degree of unconsciousness, the duration of the coma and the presence of infection. These four factors are of the greatest importance in determining the ultimate prognosis for a patient in diabetic coma.

Immediately after the patient has been admitted to the hospital the values for blood sugar and the carbon dioxide-combining power of the plasma should be determined, but one need not wait for the laboratory data before administering the initial dose of insulin as no time should be sacrificed in the treatment of a comatose patient. The amount of insulin required for the initial injection can be gaged fairly well by clinical observation and a consideration of the preceding factors. The first dose usually varies between 30 and 100 units, the initial dose

usually is approximately 40 units. As a rule, if no improvement is observed within thirty minutes after the first injection, the same dose is repeated, and smaller doses are administered frequently thereafter. Hypoglycemia is to be avoided, especially in those cases in which circulatory failure is imminent. It is in such cases that the laboratory data become essential. Insulin administered subcutaneously usually suffices, but occasionally it is necessary to administer it intravenously. This is the method of choice in a case in which the patient is shocked severely and the circulation is failing rapidly.

*Insulin Allergy*—When encountered in diabetic coma, insulin allergy presents a problem designed to tax the skill of the most ingenious clinician. This occurred in 3 cases in this series, but fortunately the circumstances were such that none of the patients was in immediate danger.

The first patient (case 80) was a woman who had mild diabetes which responded to the qualitative restriction of diet alone. One year before, at the time the diabetes had been discovered, she had experienced a generalized reaction when insulin was administered. A few days prior to her admission to the hospital acute empyema of the gallbladder had developed, and it had been feared that the necessary surgical operation might precipitate diabetic coma. In the few days between her admission to the hospital and the day of operation she was given intradermal tests for several different brands<sup>36</sup> of insulin, but all produced marked local and generalized reactions within five minutes, so that it became necessary to administer epinephrine. A sixth brand of insulin<sup>37</sup> in diluted doses was later tolerated without systemic effects although with marked local irritation of the skin. As was anticipated, acidosis developed the day after operation, the value for the carbon dioxide-combining power of the plasma decreasing to 21 volumes per cent. Desensitization to the sixth brand of insulin was attempted. A dilution of 0.5 cc of 80 unit insulin with 4.5 cc of physiologic solution of sodium chloride was made, and this was given in doses of 1 minim (0.06 cc) at first. This dose was gradually increased thereafter to 25 minims (1.54 cc) and was administered at frequent intervals. The response to this treatment was as follows. Prior to the operation the value for sugar was 250 mg per hundred cubic centimeters of blood and that for the carbon dioxide-combining power of the plasma was 42 volumes per cent. Treatment was commenced on the day following the operation, at which time the value for sugar was found to be 310 mg per hundred cubic centimeters of blood and that for the carbon dioxide-combining power of the plasma was 21 and 12 volumes per cent, respectively, on two different occasions. On the regimen of treatment just outlined, the value for sugar decreased to 190 mg per hundred cubic centimeters of blood and the carbon dioxide-combining power of the plasma increased to 55 volumes per cent. Before leaving the hospital the patient was able to tolerate the undiluted crystalline insulin, although the injection still caused a local reaction.

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36 Insulin-Lilly, Lilly's special insulin (prepared from the pancreas of the calf), Insulin-Squibb, Insulin-Stearns and insulin prepared from the pancreas of the sheep.

37 Toronto crystalline insulin.

In a second case generalized urticaria developed after large doses of insulin were administered. In a third case a marked reaction to ordinary insulin occurred, but fortunately special insulin obtained from the pancreas of calves produced no local or general reaction.

*Accessory Measures in the Treatment of Diabetic Coma*—The patient in diabetic coma is usually in shock and nearly always shows advanced dehydration. Therefore, it is of prime importance that treatment directed to combat these conditions should be instituted with a minimum of delay.

A subnormal temperature is the rule in a patient in coma, so warmth must be supplied by sufficient blankets and hot water bottles.

Dilatation of the stomach is a frequent accompaniment, and gastric lavage is often desirable. Lavage with from a 2 to 5 per cent solution of sodium bicarbonate has been employed, leaving from 200 to 300 cc in the stomach. A cleansing enema is desirable. Stimulants are often necessary, and caffeine sodobenzoate and digitalis must be administered in many cases. The value of iodine in the treatment of diabetic coma complicated by hyperthyroidism has been mentioned.

The dehydration was combated by the administration of physiologic solution of sodium chloride by the subcutaneous, rectal or intravenous route. Fluids were given hourly by mouth in quantities of from 100 to 200 cc during the first twenty-four hours, provided the coma had been relieved and nausea and vomiting were no longer present. The average total intake of fluid in cases in which this was accurately recorded was 2,658 cc in the first twenty-four hours after the patient's admission to the hospital. In cases in which the initial value for blood sugar was only moderately elevated but the alkali reserve was markedly decreased, it has seemed to be advantageous to substitute the "10 to 1 solution" (10 per cent solution of dextrose in 1 per cent solution of sodium chloride) for the physiologic solution of sodium chloride usually administered in intravenous infusions. This substitution frequently has been made in cases of threatened renal block. Fullerton, Lyall and Davidson<sup>24</sup> and others have successfully employed a hypertonic solution of dextrose intravenously (as much as 25 per cent dextrose) in the treatment of anuria following diabetic coma.

*The Use of Alkalis in Diabetic Coma*—Writers on diabetes appear to be in fair agreement on the treatment of coma, except in the matter of the use of alkalis. Around this much debated question a sharp division of opinion has arisen. Clinical and experimental data support the views of both the proponents and the opponents. Many of the arguments are based on conjecture and opinion, and the truth of the matter is still unsettled.

Starí and Fitz<sup>29</sup> have shown that in a certain proportion of cases of diabetes mellitus the amount of undetermined organic acid (later shown by Himwich to be lactic acid) excreted in the urine is much greater than the amount of ketone bodies. Particularly is this true in cases of severe acidosis without ketonuria in which the decrease in the value for the carbon dioxide-combining power of the plasma is much greater than can be accounted for by the molecular concentration of the acetone bodies in the blood. They have concluded that alkalis are urgently required in such cases, as insulin will not affect the acidosis which is the result of acids other than the ketone bodies. Allen and Wishart,<sup>35</sup> as a result of experimental work on acidosis in dogs, concluded that acetone bodies alone were not responsible for the disorder. Hartman and Darrow<sup>38</sup> reported a comparative study of the composition of the plasma in cases of severe diabetic acidosis and the changes taking place during recovery when the patient had been treated with insulin and physiologic solution of sodium chloride with and without sodium bicarbonate and found that the normal values for the carbon dioxide-combining power of the plasma and the hydrogen ion concentration were restored slowly by the use of insulin and fluids alone while the administration of sodium bicarbonate with insulin and physiologic solution of sodium chloride provided "a rapid, safe, and complete relief from acidosis." They also commented on the remarkable relief from hyperpnea which follows the administration of alkalis. Bowen and Hekimian supplemented the treatment of coma in 76 per cent of their cases with proctoclysis of 5 per cent solution of sodium bicarbonate. They said that the average patient with diabetic coma "apparently does not require alkalis to make a satisfactory recovery, but it has been our clinical impression that cases respond faster and they are more readily relieved of hyperpnea, which is often distressing, when alkalis are used."

I have found no writer who insists on the administration of sodium bicarbonate as a routine therapeutic measure in the treatment of coma, its use is reserved for certain patients as the indications present.

In the preinsulin era the treatment of diabetic acidosis was almost entirely dependent on the administration of alkali, and in that period alkalis were frequently administered in what now would be considered enormous doses. In 1913 Blum<sup>39</sup> called attention to tetany without disturbance of the amount of calcium and phosphorus in the blood serum which resulted from such treatment.

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38 Hartman, A. F., and Darrow, D. C. Chemical Changes in the Body Occurring as the Result of Certain Diseases. III. The Composition of the Plasma in Severe Acidosis and the Changes Taking Place During Recovery. *J. Clin. Investigation* 6: 257-276 (Oct.) 1928.

39 Blum, L. Symptomatologie und Therapie des Coma diabeticum. *Ergebn. d. inn. Med. u. Kinderh.* 11: 442-491, 1913.

Haldane and his co-workers<sup>40</sup> showed that when alkalis are administered to a patient with acidosis more acid appears to be liberated. This also was demonstrated to be true of a normal subject. These workers have concluded that the administration of alkalis interferes with the combustion of carbohydrates. Mosenthal and his associates<sup>41</sup> expressed the belief that removing acids from the blood by the use of alkalis may injure vulnerable kidneys because of the resulting irritation.

Joslin and his co-workers have consistently argued the negative side of the issue and have pointed with pride, and well they may, to their low mortality of 12.7 per cent in cases of diabetic coma. None of their patients has received any alkali since 1917. Therefore, in 1929 they stated "we shall not give alkalies for diabetic coma in our clinic and thus advice we shall continue to give to other physicians until those who advocate alkalies report a comparable series of cases with better results than our own."<sup>42</sup> I believe it is incorrect, however, to attribute their excellent results to the fact that alkalis were not administered. Perhaps these results are more likely attributable to the prompt and energetic treatment and the meticulous attention to detail exerted in the care of comatose patients by the clinicians of the New England Deaconess Hospital. Blackfan<sup>42</sup> likewise has obtained excellent results in the treatment of coma in children without the use of sodium bicarbonate.

The series of cases of diabetic coma reported by Bowen and Hekimian, in 1930, although not as large as Joslin's series, presents the answer of the proponents of alkalis. In their 81 cases of coma (carbon dioxide-combining power not exceeding 15 volumes per cent) sodium bicarbonate was administered by proctoclysis, lavage and occasionally intravenously to 76 per cent of the patients. The mortality was exceedingly low—only 12.4 per cent.

The opinion of Dr. R. M. Wilder and his associates at the Mayo Clinic regarding the use of alkalis has been somewhat neutral, but within recent years it has definitely turned toward the use of alkalis in selected cases. Alkalis are not necessary as a routine measure but are definitely effective in certain cases. Two cases will serve to illustrate this point.

CASE 79—A boy aged 11 years was admitted to the hospital at 5 a. m. The value for sugar was 380 mg. per hundred cubic centimeters of blood and that for the carbon dioxide-combining power of the plasma was only 2 volumes per cent.

40 Haldane, J. B. S., Wigglesworth, V. B., and Woodrow, C. E. The Effect of Reaction Changes on Human Carbohydrate and Oxygen Metabolism, *Proc. Roy. Soc., London*, s. B. **96** 15-28 (Feb. 1) 1924.

41 Mosenthal, H. O., Killian, J. A., and Myers, V. C. Value of Sodium Bicarbonate in Treatment of Diabetes Mellitus, *J. A. M. A.* **78** 1751 (June 3) 1922.

42 Blackfan, quoted by Joslin, Root and White.<sup>1a</sup>

By 11 a m, although sufficient insulin had been administered to reduce the value for blood sugar to normal, the value for the carbon dioxide-combining power of the plasma had increased to only 12 volumes per cent. Within the next few hours more insulin was given, together with a 5 per cent solution of dextrose, but this also failed to increase the alkali reserve appreciably, to suppress hyperpnea or to restore consciousness, although the value for blood sugar had remained practically within normal limits for ten hours. It then was decided to administer 300 cc of a 5 per cent solution of sodium bicarbonate intravenously. The extreme hyperpnea was relieved within an hour, and the mental change was readily apparent. This injection was followed by the oral administration of 3 Gm of sodium bicarbonate every second hour for three doses.

The administration of insulin promptly reduced the hyperglycemia in this case, but it was totally ineffective in relieving the acidosis or coma. It is therefore logical to assume that this case probably represented one of those in which undetermined organic acid (lactic acid, according to Himwich) is more responsible for the acidosis than are the ketone bodies. In such cases alkalis are not only indicated but may be needed urgently.

CASE 75—A woman aged 59 was admitted to the hospital at 10 a m in deep coma. The value for sugar was 534 mg per hundred cubic centimeters of blood, and that for the carbon dioxide-combining power of the plasma was 13 volumes per cent. On account of distressing hyperpnea it was decided to supplement insulin with sodium bicarbonate intravenously. Accordingly, 400 cc of a 5 per cent solution of sodium bicarbonate was slowly injected. It was apparent to all observers that the hyperpnea was relieved after only 200 cc of the solution had been injected. By 2 p m the value for sugar was 245 mg per hundred cubic centimeters of blood, and that for the carbon dioxide-combining power of the plasma was 44 volumes per cent and the patient definitely was out of coma.

In 49 (45 per cent) of the cases in this series alkalis were used, but as 15 of the patients received sodium bicarbonate only by mouth and in almost negligible amounts, only 34 patients (31 per cent) received alkalis in effective doses by lavage, proctoclysis or intravenous administration.

The dose of sodium bicarbonate which was employed was never large enough to provoke any untoward results. More than 500 cc of a 5 per cent solution of sodium bicarbonate has never been administered intravenously, but this dose frequently has been supplemented by the administration of sodium bicarbonate by proctoclysis or by leaving from 100 to 200 cc of a 5 per cent solution of sodium bicarbonate in the stomach after lavage. The average total dose of sodium bicarbonate has been from 25 to 40 Gm. This was exceeded in only 5 cases. There is little doubt that many of the objectionable results from the administration of alkalis in cases of diabetic coma can be attributed to overdosage. When this is avoided and a proper selection of cases is made, ill effects are infrequently observed.

I suggest that the following factors are indications for the administration of alkalis in diabetic coma (1) the presence of distressing hyperpnea, (2) the presence of a deeply depressed alkali reserve, especially when the value for the carbon dioxide-combining power of the plasma is less than 10 volumes per cent, and (3) in the cases in which the administration of insulin is ineffective in elevating the carbon dioxide-combining power of the plasma or in relieving the stupor, although it may be normally effective in reducing the hyperglycemia

#### SUBSEQUENT CLINICAL COURSE

Eighty of Joslin's 276 instances of diabetic coma occurred among 33 patients who had had two or more attacks of coma. Ralli and Waterhouse<sup>43</sup> have reported the case of a 16 year old girl who finally succumbed to coma after having been admitted to the hospital 19 times because of either marked acidosis or coma. Patients who have had frequent attacks of coma will be found in any large series of cases. Fifty per cent of the 82 patients in this series who were traced had experienced other attacks of coma either before or subsequent to their initial visit to the clinic. One patient survived five attacks of coma only to succumb to the sixth.

Children, for obvious reasons, more frequently have repeated attacks of coma than do adults. Six of the 9 patients who were treated at the clinic more than once for coma were children.

The second attack of coma is likely to be of a more severe grade than the first. More than twice as much insulin was required in the first twenty-four hours of the second attack than was required in the same period in the first attack in the 9 cases in which the patients had more than one attack of coma. Likewise, the value for blood sugar when the patient was admitted to the hospital was higher in the succeeding attack than it was in the first attack in 7 of these 9 cases.

#### ULTIMATE PROGNOSIS AND CAUSE OF DEATH

Thirty-nine of the 99 patients who comprise this series have died, 50 were living at a recent date and 10 could not be traced. The 39 deaths comprise the 17 patients who died at the hospital and the 22 who died elsewhere from one week to eleven years after leaving the clinic.

Thirty of the 50 living patients rate their health as excellent, 20 say that it is fair. Few of these patients have suffered from acute illnesses other than the diseases of childhood. A few have undergone operations. One patient was reported to have died from "spinal

<sup>43</sup> Ralli, Elaine P., and Waterhouse, Alice M. Diabetic Coma Occurring Nineteen Times in the Life of a Patient with Diabetes Mellitus, *J. Lab. & Clin. Med.* **18** 1119-1127 (Aug.) 1933.



meningitis," but in view of the fact that he was suffering from active pulmonary tuberculosis when under observation at the clinic, it seems more probable that he succumbed to tuberculous meningitis. This apparently was the only patient in the entire series who had active tuberculosis either before or after an attack of coma. This is in marked contrast to the experience reported by Root,<sup>44</sup> of Joslin's clinic, who found that 8 per cent of the patients who recovered from coma revealed evidence of tuberculosis within three years. Wilder<sup>45</sup> has reported that the records of 3,793 consecutive cases of diabetes mellitus at the Mayo Clinic showed active tuberculosis in only 37, an incidence of less than 1 per cent.

TABLE 6—*Causes of Death in Cases of Diabetic Coma*

	Fatalities in Hospitals in Rochester	Fatalities Elsewhere	Total
Uncomplicated diabetic coma	3	8	11
Cardiovascular disease	4	1	5
Pneumonia and its complications	2	2	4
Bilateral pyelonephritis with metastatic abscesses	1		1
Septicemia	1		1
Erysipelas	1		1
Acute yellow atrophy and toxic nephrosis (arsenical?)	1		1
Hodgkin's disease	1		1
Hemochromatosis	1		1
Diabetic gangrene	1		1
Advanced pernicious anemia and coma	1		1
Carcinoma (sigmoid flexure)*		1	1
Meningitis, tuberculous (?)		1	1
Acute pancreatitis†		1	1
Addison's disease‡		1	1
Intestinal hemorrhage from unknown cause		1	1
Heat prostration		1	1
Cause unknown		5	5
Total	17‡	22	39

\* Diagnosis confirmed by operation at the clinic

† Diagnosis verified by necropsy elsewhere

‡ Diagnosis verified by necropsy in 14 cases

The causes of death in the cases in which coma proved fatal are given in table 6. The clinical diagnosis was confirmed by necropsy in 14 of the 17 cases in which death occurred at the clinic, and either by necropsy or operation in 3 of the 22 cases in which death occurred elsewhere. It will be seen that uncomplicated diabetic coma was responsible for 11 deaths, 8 of which occurred after the patient had left the clinic. In the majority of cases of uncomplicated coma in which death occurred elsewhere, the patients were elderly, and it is likely that cardiovascular disease may have played more of a lethal rôle than the

44 Root, H. F. quoted in Joslin, E. P. *A Diabetic Manual for the Mutual Use of Doctor and Patient*, Philadelphia, Lea & Febiger, 1934, p. 125.

45 Wilder, R. M. *Diseases of Metabolism*, in Musser, J. H. *Internal Medicine: Its Theory and Practice in Contributions by American Authors*, ed. 2, Philadelphia, Lea & Febiger, 1934, pp. 993-1002.

figures reveal. However, cardiovascular disease was listed as the cause of death in only 5 cases. Pneumonia and its complications were responsible for 4 deaths, but the mortality probably is no higher than would have been noted in a similar group of nondiabetic persons. Diabetic gangrene, hemochromatosis, acute pancreatitis and Addison's disease were each responsible for 1 death, but with these exceptions, the other causes of death bore no relationship to diabetes, and the deaths resulted from a wide variety of diseases.

#### SUMMARY

One hundred and eight instances of diabetic coma in 99 patients who were seen at the Mayo Clinic between October 1923 and January 1934 are reviewed. In all except 3 of these cases the value for the carbon dioxide-combining power of the plasma was 25 volumes per cent or less when the patient was admitted to the hospital. There were 17 deaths, or a mortality of 15.7 per cent in the 108 cases. The mortality in the first four decades of life was 4 per cent, in the next four decades, 40 per cent. Only 3 patients died of uncomplicated coma. Death in these cases occurred within two, ten and fifteen hours, respectively, after the patient's admission to the hospital. The largest number of cases of coma occurred in the summer months and more occurred in August than in any single month. Among the patients who were less than 40 years of age the distribution by sex was practically equal, but 70 per cent of those over 40 years of age were women. One patient, aged 74, recovered. The average duration of diabetic symptoms before the onset of coma was twenty-six and five-tenths months. In 51 per cent of the cases coma developed in the first year of diabetes.

The factors precipitating the diabetic coma have been determined. Dietary infractions, omission of insulin and infection were the precipitating factors in 83 per cent of the cases. The value of the Kussmaul type of breathing, the degree of unconsciousness, the state of the circulation and the ocular findings in coma are discussed. The frequency with which the symptoms of uncomplicated diabetic acidosis may simulate those of acute surgical disease of the abdomen is revealed. Illustrative cases are reported.

There is a surprising lack of correlation between the value for blood sugar and that for the carbon dioxide-combining power of plasma with the severity of the coma. The ultimate prognosis and the amount of insulin required to relieve coma are more dependent on the age of the patient, the degree of unconsciousness, the duration of the coma and the presence of infection than they are on the data obtained on laboratory examination. The 2 patients who showed a carbon dioxide-combining power of the plasma of only 2 volumes per cent recovered.

The gravity of a high concentration of urea in the blood and anuria in diabetic coma is emphasized. Three cases in which ketonuria was absent are reported.

The treatment of coma as conducted in these cases is described. The indications for the administration of sodium bicarbonate are given. Allergy for insulin presents a serious complication. It was present in 3 patients. In this series 22 have died since leaving the clinic, which, with the 17 patients who died in the hospital, gives a total of 39 deaths in the entire group. The causes of death here and elsewhere are enumerated. Coma, cardiovascular disease and pneumonia accounted for more than half of them. Conspicuous for its absence was tuberculosis, which was a complicating disease in only 1 case, of the 50 patients known to be living, none has any knowledge of having tuberculosis.

# SYNCOPE AND CONVULSIONS DUE TO A HYPER- ACTIVE CAROTID SINUS REFLEX

DIAGNOSIS AND TREATMENT

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For many years it has been known that pressure over the vagus nerve produces slowing of the heart<sup>1</sup> Not until 1923, however, was the true mechanism of this phenomenon recognized Hering<sup>2</sup> conclusively demonstrated in animals that slowing of the heart and other effects of such pressure are due to reflexes arising in the carotid sinus His work has been amply confirmed, particularly by Heymans<sup>3</sup> The application of these findings to man has been rather recent A report of fifteen cases by Weiss and Baker<sup>4</sup> demonstrated that an abnormally sensitive carotid sinus mechanism can be responsible for attacks of unconsciousness and convulsions and that such attacks can be reproduced by pressure over one carotid sinus In most of the fifteen patients the attacks were associated with cerebral anoxemia resulting either from cardiac asystole or from a primary reflex depression of the blood pressure In two patients, however, unconsciousness occurred in the absence of change in either the heart rate or the blood pressure We

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1 Waller, A Experimental Researches on the Functions of the Vagus and the Cervical Sympathetic Nerves in Man, *Proc Roy Soc London* **11** 302, 1860-1862 Czermak, J Ueber mechanische Vagus-Reizung beim Menschen, *Jenaische Ztschr f Med u Naturwissensch* **2** 384, 1865-1866

2 Hering, H E Die Karotissinusreflexe auf Herz und Gefasse, Dresden, Theodor Steinkopff, 1927

3 Heymans, C Le sinus carotidien et les autres zones vasosensibles réflexogènes, Paris, Presses Universitaires de France, 1929

4 Weiss, Soma, and Baker, J P The Carotid Sinus Reflex in Health and Disease Its Rôle in the Causation of Fainting and Convulsions, *Medicine* **12** 297, 1933

have recently reported studies of twenty-one cases of that type <sup>5</sup> A more detailed account of the various symptom complexes and hypersensitive carotid sinus reflexes in man, which have come to be known as the carotid sinus syndrome, can be found in these reports

#### THE CAROTID SINUS SYNDROME

According to present knowledge, a hypersensitive state of the carotid sinus reflex may produce unconsciousness, convulsions or milder manifestations, through one or more of three main reflex arcs Broadly speaking, both the afferent and the efferent arm of these reflex arcs lie within the confines of the autonomic nervous system The afferent, or sensory, limb is probably always the same, but the motor pathway differs in various subjects The stimulus originates chiefly in the bulbous dilatation at the bifurcation of the common carotid artery, known as the carotid sinus <sup>2</sup> This stimulus may take the form of a stretch by distention from within the artery or of a relaxation by shrinkage of the arterial content Frequently, hormones or other chemical substances act as powerful stimuli on the remarkably sensitive end-organs within the arterial wall Furthermore, it is probable that end-organs capable of receiving these specialized stimuli are also present in adjoining parts of the arterial wall and may even occur in other blood vessels Impulses which result from such stimuli then travel centrally along a variety of pathways to the medulla The chief afferent pathways are the inter-carotid, the glossopharyngeal and the hypoglossal nerves, as well as the vagus nerve and the cervical portion of the sympathetic chain <sup>6</sup> On reaching the brain stem the sensory impulse traverses the central synapses and after crossing passes contralaterally as a motor impulse toward the periphery through rather widespread autonomic nerve pathways It is the variation in the peripheral distribution of the abnormally powerful motor impulses, with the resultant activity, that differentiates the types of symptoms included in the carotid sinus syndrome <sup>5</sup> The type of response elicited by the stimuli traveling over the nerve pathways depends, then, primarily on the location of the motor responses induced In man the three motor pathways responsible for syncope involve the vagus nerve, the vasomotor-depressor nerves or the central motor pathways They also commonly appear in a mixed form, and the type of syncope is then classified in accordance with the dominant motor pathway involved

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5 Ferris, E B, Jr, Capps, R B, and Weiss, Soma Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions A Study of Thirty-Two Additional Cases, *Medicine* **14** 377, 1935

6 Braeucker, W Das pressorezeptorische Nervensystem und seine praktische Bedeutung in der Chirurgie, *Beitr z klin Chir* **158** 309, 1933

In normal subjects mechanical stimulation of the carotid sinus does not produce symptoms, and physiologic stimulation induced from within the sinus by varying the intrasinus pressure produces a specific effect, namely, a slight and temporary change in the peripheral blood pressure. In patients in whom the carotid sinus reflex mechanism is abnormally sensitive, however, mechanical stimulation causes marked symptoms and intrasinus stimulation induces many symptoms in addition to the specific effect on the blood pressure. Likewise, chemical stimulation of the sinuses of such patients induces abnormal manifestations. Thus an abnormal response of the carotid sinus may be brought about by one of several stimuli and may take one of several forms. Abnormal afferent impulses may arise from the carotid sinus as the result of normal stimulation in instances in which the sinus is hypersensitive. Furthermore normal afferent impulses from the sinus may set up abnormal reactions as the result either of changes in the threshold of the central synapses or of increased sensitivity of the motor arm of the reflex arc resulting from disease. Any combination of these three factors may play a rôle in individual cases. The observations reported previously<sup>7</sup> reveal that a hyperactive carotid sinus reflex may be either unilateral, involving one sinus only, the activity of the other reflex remaining normal, or bilateral. If the reflexes of both carotid sinuses are hyperactive, the degree of sensitivity usually differs.

The motor pathways taken by impulses from the carotid sinus may be diverse in abnormal conditions. We have been primarily interested in the motor responses that induce fainting, that is, the vagal, depressor and central responses. In the fifty-two patients<sup>8</sup> studied we encountered, however, a number of motor manifestations causing symptoms not directly related to syncope. These manifestations accompanied the spontaneous attacks and could be reproduced by mechanical stimulation of the carotid sinus. The signs and symptoms produced in our patients are listed in detail in table 1, in the order of their frequency.

*The Three Types of Carotid Sinus Syndrome*—As previously pointed out, the dominant motor pathway of a hypersensitive carotid sinus reflex determines the classification of the condition as of one of three types. The first is the vagal type, in which the symptoms, particularly the dizziness, fainting and weakness, result from cardiac asystole. The asystole is due either to sinu-auricular or to auriculoventricular block, which in its turn produces acute cerebral anoxemia. In its pure form the efferent response travels over the vagus nerve to set up a heart block. Associated with it is a fall in blood pressure. An attack with all its characteristics can be reproduced by firm pressure and

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<sup>7</sup> Weiss and Baker<sup>4</sup>; Ferris, Capps and Weiss<sup>5</sup>

<sup>8</sup> This series does not include the fifteen cases reported by Weiss and Baker<sup>4</sup>

massage for from fifteen to thirty seconds over the sensitive sinus at the bifurcation against the transverse processes of the cervical portion of the spine. Only one sinus should be stimulated at a time, and the test should preferably be performed with the patient sitting or standing. The attack can be abolished within three minutes by the intravenous administration of 1 mg. of a solution of atropine sulfate, which paralyzes the vagal endings, thus preventing reflex cardiac slowing. Eight minims (0.5 cc.) of a solution of epinephrine hydrochloride administered subcutaneously prevents the attacks, through its local stimulating effect on the ventricles.

The second, or depressor type of carotid sinus syndrome is the least common of the three and usually appears in association with one of the other two types. Indeed, we have observed it in pure form only twice.

TABLE 1—*Signs and Symptoms in Patients with the Carotid Sinus Syndrome*

Symptom	Frequency			
	Entire Group	Cerebral Type	Vagal Type	Depressor Type
Fainting	52	33	17	2
Dizziness and weakness	52	33	17	2
Hyperpnea	48	30	17	1
Pallor of the face	48	29	17	2
Bradycardia (slight to moderate)	26	24	0	2
Bradycardia (asystole)	17	0	17	0
Numbness and tingling of the extremities	25	16	9	0
Convulsions	24	11	13	0
Drowsiness	13	9	4	0
Cataplexy	9	8	1	0
Epigastric distress	8	7	1	0
Nausea	7	5	2	0
Lacrimation	5	5	0	0
Cough	4	1	3	0
Amnesia	3	2	0	0
Palpitation	3	3	0	0

The afferent impulse is set up, as in the vagal type, from the carotid sinus, while the efferent impulse acts on small blood vessels by way of the aortic depressor nerves. The symptoms result from primary reflex vasodilatation and secondary depression of the blood pressure, entirely unrelated to cardiac slowing or any form of cardiac arrhythmia. The clinical manifestations are brought about, nevertheless, by cerebral anoxemia resulting from a diminution in the flow of blood to the brain. Spontaneous attacks can be reproduced in the same manner as in cases of the vagal type of syncope. Atropine, however, has no effect on the signs or symptoms, since they do not result from cardiac slowing. On the other hand, epinephrine in the dosage previously mentioned promptly aborts the attack, through its constricting action on the small blood vessels.

The third type of carotid sinus syndrome is the cerebral type. In it the symptoms result apparently from impulses which travel directly to the brain. No significant change occurs in the heart rate or the blood

pressure, and the total flow of blood through the brain is normal during the phase of the attack in which the patient is unconscious<sup>5</sup> As in the other types, the afferent impulses arise in the carotid sinus Evidence suggests that these impulses travel to the medulla and are distributed from there as motor impulses directly to certain vegetative centers in the region of the hypothalamus or to the blood vessels which supply such areas Attacks can be reproduced as previously described, subjective rather than objective findings being prominent The attacks may be induced within as short a period as five seconds Neither atropine nor epinephrine aborts or relieves the cerebral type of attack Treatment of the sinus with procaine hydrochloride, however, makes the local stimulus ineffective

*Clinical Manifestations*—Attacks of unconsciousness, with or without convulsions, which occur at intervals varying from days to months are the commonest complaint The attack is usually preceded by sensations of dizziness, weakness, ringing in the ears or epigastric distress, but occasionally there are no premonitory symptoms Between attacks of syncope most patients experience frequent milder attacks which consist of dizziness, weakness or sensations of numbness and tingling of the extremities The symptoms almost always occur when the patient is in the upright position and are relieved by his lying down when premonitory symptoms occur The attacks may be related to such factors as sudden movements of the neck, pressure against or blows on the neck and sudden changes in position of the head from horizontal to vertical or vice versa Factors such as fatigue, emotional upsets and menstruation may precipitate the symptoms In many cases, however, no such cause can be ascertained Unconsciousness lasts from one to three minutes, and the patient feels well after recovery, except for headache or continued dizziness in rare instances In only one case did we observe that the patient felt weak for about a day following both a spontaneous and a single induced syncope In this case the unique observation was made that in spite of cardiac slowing the arterial blood pressure was elevated after the syncope There was a striking resemblance between the postsyncopal state of the patient and the condition of a patient under the effect of large doses of epinephrine

Biting of the tongue and incontinence of urine have each been observed only once Hyperpnea is usually associated with an attack, but apnea may occur Nausea with actual vomiting occurred in one patient after stimulation of the carotid sinus The symptoms which may be associated with attacks are presented in table 1 All these symptoms, once they have occurred in an attack, can be regularly elicited later by pressure over the carotid sinus Depending on the intensity of the stimulus, mild or severe manifestations can be elicited and their



progress stopped at almost any stage by discontinuing the stimulation. When an attack is induced by the application of pressure to one sinus, pallor of the face as a rule precedes unconsciousness. When convulsions occur they usually begin first in the extremities contralateral to the sinus being stimulated and then become generalized.

Local lesions of the sinus or general disease was found in the majority of our patients (table 2). Of particular interest in this connection is the fact that seven of the seventeen patients subject to the vagal type of syncope there was clinical evidence of degenerative change in the heart, and in the group as a whole there was a high incidence of generalized cardiovascular change.

Four cases of digitalis intoxication were encountered associated with spontaneous and induced attacks. The sensitizing effect of digitalis on the carotid sinus reflex is of considerable importance from a clinical point of view, as we have previously pointed out.<sup>5</sup> When digitalis is administered to elderly patients with coronary disease who complain of spells of weakness or dizziness, on the false assumption that such symptoms are due to cardiac failure, it is likely to aggravate their symptoms. Furthermore, from a theoretical point of view the routine pre-operative use of digitalis to prevent cardiac failure is contraindicated unless there is definite evidence of failure. The use of this drug in combination with the administration of volatile anesthetics and the usual manipulation about the neck coincident with anesthesia is likely to be responsible for such operative complications as temporary vasomotor collapse, cardiac arrhythmia or sudden death.

Various grades of neurosis were manifest in several patients. Nine appeared to have a mild type, which was classified by us as neurasthenia. Others showing neurotic stigmas proved to have a low basal metabolic rate not due to hypothyroidism.<sup>5</sup> In one of six patients suffering from definite severe neurosis the basal metabolic rate was 0 per cent, and it ranged from minus 17 to minus 25 per cent in the other five. In general, the vagal and the depressor type of syncope predominate in patients having degenerative disease, and these two types are equally distributed in patients having neurosis. Mild neurosis is frequently present in patients subject to the cerebral type of syncope. The similar behavior of the carotid sinus reflex mechanism in patients with organic disease and in persons with visceral neurosis is of much interest, as it demonstrates the fact that often for identical clinical manifestations the same physiologic mechanism may be responsible in instances of organic and functional disease.<sup>9</sup>

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9 Weiss, Soma. The Interaction Between Emotional States and the Cardiovascular System in Health and in Disease, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 3, p. 1181.

## DIAGNOSIS

The diagnosis of carotid sinus syncope is applied to short attacks of syncope and related manifestations which usually develop when the patient is in the upright position and which can be reproduced with regularity by means of mechanical stimulation of the carotid sinus. Treatment of the sinus with procaine hydrochloride abolishes the effects of stimulation.

Both sinuses should never be stimulated simultaneously. If the response is sufficiently abnormal, a typical reaction occurs after from five to thirty seconds of pressure on one sinus. Improper technique in the execution of the pressure and massage has been, according to

TABLE 2—*Diseases of Thirty-Six Patients with the Carotid Sinus Syndrome and the Age Distribution of Fifty-Two Patients*

Disease	Entire Group	Cerebral Type	Vagal Type	Depressor Type
Local abnormality in the region of the carotid sinus	31	19	10	2
Dilated sinus	21	11	8	2
Cervical adenitis	17	14	3	0
Recurring cervical adenitis	4	3	1	0
Local sclerosis of the sinus	9	2	5	2
Local cardiac abnormality	16	6	8	2
Systemic disease	36	19	15	2
Hypertension	16	8	6	2
Arteriosclerosis	10	3	5	2
Vegetative neurosis	8	5	3	0
Dietary deficiency	7	3	4	0
Dermatographia	5	5	0	0
Disturbance associated with the menopause	5	4	1	0
Raynaud's disease	4	4	0	0
Digitalis intoxication	4	1	3	0
Syphilis of the central nervous system	4	3	1	0
Age				
Average	45.6	41.6	50.9	69.0
Lowest	13	13	24	64
Highest	74	72	72	74

our experience, the usual cause for failure to reproduce an attack in cases in which it is suspected that syncope is due to a hyperactive carotid sinus reflex. To ascertain the location of the sinus it is advisable to extend the head. This position throws the sinus forward so that as a result it can be easily palpated. One should be certain that the carotid sinus remains under the palpating fingers during pressure and should remember that the bifurcation may be located either above or considerably below its usual position in the neck. We have observed patients in whom the sinus was situated along the lower end of the larynx rather than at its usual location along the angle of the jaw. As an attack occurs more readily when the patient is in the upright than when he is in the horizontal position, the test should be performed with him sitting or standing. Hysteroneurosis can be differentiated by infiltrating the region of the sensitive sinus with a 1 per cent solution of procaine hydrochloride. This abolishes the induced attack in patients suffering

from the true syndrome. Likewise, suggestion, occlusion of the carotid artery below the sinus and pressure over various other areas should not initiate a typical seizure.

When symptoms similar to those occurring in association with the carotid sinus syndrome are due to other causes, they cannot be reproduced by stimulation of the carotid sinus and they can be ruled out with the aid of the tests described. The carotid sinus syndrome may simulate atypical petit mal, grand mal or a narcoleptic or a cataleptic seizure, but these types of attack cannot be induced by stimulation of the carotid sinus.

It has been pointed out that the response of the carotid sinus in patients suffering from epileptic seizures is normal.<sup>4</sup> Similarly, we have found no relationship between the behavior of the carotid sinus reflex and postural hypotension. The relationship of carotid sinus syncope to other types of syncope has been discussed recently by Weiss.<sup>10</sup> His observations indicate that with rare exceptions carotid sinus syncope occurs independently of other types of syncope, that is, the hypersensitive state of this reflex is usually present without abnormality of any other mechanism responsible for fainting. Contrariwise, in other types of syncope the carotid sinus reflex is usually normal.

The type of carotid sinus reflex mechanism responsible for the symptoms in a case can be determined by observing the heart rate and the blood pressure during an induced attack and by the use of atropine sulfate and epinephrine or ephedrine. A solution of atropine sulfate given intravenously in a dose of 1 mg ( $\frac{1}{60}$  grain) abolishes the vagal reaction within three minutes but does not alter the depressor or the cerebral reaction. A subcutaneous injection of 0.5 cc (8 minims) of a solution of epinephrine hydrochloride (1:1,000) abolishes both the vagal and the depressor reaction but does not alter the cerebral reaction. In patients having a mixed reaction it is important to determine the dominant type by the use of these drugs.

We have contrasted the behavior of patients with a hypersensitive carotid sinus with the response of normal subjects. If the patient is suffering from spontaneous manifestations of the reflex, the contrast is indeed striking. This does not imply, however, that cases in which the behavior is intermediate between normal and grossly pathologic do not occur. Such instances are frequent, but they are outside the scope of this discussion. Similarly, the intensity of the stimulus is of importance. A powerful blow to the carotid sinus results in syncope ("knock out") even when the reflex is normal.

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10 Weiss, Soma. Syncope and Related Syndromes, in Christian, H. A., and Mackenzie, J. Oxford Medicine, London, Oxford University Press, 1935, vol. 2, chap. 8 A, p. 250.

## TREATMENT

*General Measures*—General treatment consists in correcting all associated abnormalities if possible. For elderly patients suffering from degenerative disease few beneficial measures can be taken, but for many other patients the symptoms can be lessened or relieved entirely by correcting the accompanying pathologic conditions. We have completely relieved one patient by the treatment of tuberculous glands, one by antisyphilitic therapy, two by correcting a food deficiency and four by diminishing the dose of digitalis which they were taking regularly. Whenever possible other conditions which tend to bring on an attack, such as constriction from a tight collar, fatigue, emotional upsets and worry, should be eliminated. Patients should be assured that they are not suffering from epilepsy or severe heart disease as far as the symptoms of the carotid sinus syndrome are concerned.

*Specific Measures*—*Vagal Type* Since the vagal type of syndrome is due to a reflex slowing or asystole of the heart, drugs which block the vagal reflex or prevent cardiac asystole in the face of a complete heart block prevent attacks. Atropine sulfate in a dose of 0.5 mg (1/120 grain) from three to four times a day by mouth, or the equivalent of tincture of belladonna, usually prevents spontaneous symptoms. The dose should be regulated in individual cases to the smallest amount necessary to prevent symptoms, to minimize the side effects of the drug. When such effects are uncomfortable to the patient, ephedrine sulfate, 30 mg (½ grain) three times a day, may be given by mouth instead. This drug does not prevent a reflex heart block but acts directly on the ventricles, which then assume an independent rhythm fast enough to prevent symptoms whenever the heart block occurs. The dose of ephedrine should likewise be regulated according to individual requirements. If excessive nervousness or palpitation of the heart occurs, 15 mg (¼ grain) of phenobarbital given with each dose usually brings relief.

Surgical denervation of the carotid sinus, as described later, can be performed on patients who do not tolerate drug therapy and on those having a mixed type of syndrome in whom drugs do not give adequate relief.

*Depressor Type* Since fainting in patients subject to the depressor type of syndrome is due to reflex vasodilatation through the aortic depressor nerves, atropine has no effect. A threatening attack can be aborted with epinephrine and future recurrences prevented by oral administration of 15 mg (¼ grain) of ephedrine sulfate from three to four times a day, or by related drugs. As in cases of the vagal type, surgical denervation of the carotid sinus may be indicated.

**Cerebral Type** As this type of syncope is not caused by change in the heart rate, in the blood pressure or in the cerebral blood flow, drugs which alter such functions are of no benefit. If success does not attend the correction of accompanying abnormal conditions together with an adequate application of general therapeutic measures, surgical denervation of the sinus offers the only relief. It is particularly important when the patient has attacks of such frequency and severity as seriously to disrupt his normal existence.

The operation is limited to the sensitive sinus and consists in stripping the common, internal and external carotid arteries including the bifurcation, and denuding the area of its nerve supply. A 3 inch (7.5 cm) incision along the anterior border of the sternocleidomastoid muscle, with its center opposite the cricoid cartilage, is carried through the skin, the platysma and the superior cervical fascia to the muscle. The sternocleidomastoid muscle is then retracted laterally, exposing the upper end of the carotid sheath. The internal jugular vein is retracted medially and the common carotid artery exposed by dividing the sheath. The internal and the external carotid artery and the bifurcation are then exposed and stripped, the process being carried out from the periphery toward the bifurcation. Since the innervation may be widespread along the vessels, the arteries should be stripped for a distance of at least 2 cm above the bifurcation. The intercarotid tissue should be freed laterally and beneath, and isolated and divided a short distance above its attachment to the bifurcation. The tissue contains many nerve fibers, and the wall of the artery at the point where these enter is thin and friable. Unless particular care is exercised, the attempt to strip this region may result in a tear in the artery.

When the intercarotid nerve is sectioned, a distinct increase in the blood pressure and the heart rate usually occurs. The changes are temporary, and the heart rate and the blood pressure return to normal within from two to six hours. None of the ten patients on whom a unilateral denervation of the carotid sinus was performed by one of us showed a permanent alteration in the blood pressure or the heart rate. Two of these patients had moderate hypertension previous to the operation, and the tension remained unchanged. We have had no opportunity to observe the effect of bilateral denervation of the carotid sinus on the blood pressure level. We have previously suggested that a permanent rise in the blood pressure in man following such a procedure is extremely unlikely. Recent experiments on animals demonstrated that the blood pressure returns to its normal level even when both carotid nerves and in addition both aortic depressor nerves are cut.<sup>11</sup>

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11 Green, M. F., and de Groat, A. Observations on the Late Effects of Denervation of the Carotid Sinuses and Section of the Depressor Nerves, *Am J Physiol* **112** 488, 1935

**Results of Surgical Treatment** Ten patients subject to the cerebral type of syncope have been treated by surgical denervation of the sinus within the past two years. Two had a recurrence of symptoms, and eight remained free from attacks. Of the two patients in whom the treatment failed, one was well for three months but during the following two months had one attack of unconsciousness and frequent attacks of weakness. The other remained well for twelve months, and his subjective condition then reverted to its former state. The symptoms which returned in these two patients, however, were atypical as compared with the original symptoms, and studies have demonstrated that their recent attacks could not be duplicated by pressure over either carotid sinus.

It is interesting that these two patients had a basal metabolic rate of minus 20 and minus 25 per cent, respectively, and presented many stigmas of severe vegetative neurosis. The basal metabolic rates of the eight patients in whom the syndrome was cured, however, ranged from 0 to minus 11 per cent, and the degree of neurosis was slight. This suggests that the success of surgical treatment in patients with severe widespread neurosis associated with a low basal metabolic rate is doubtful and that such states contraindicate operative intervention.

#### SUMMARY

- 1 A hyperactive state of the carotid sinus reflex can be responsible for clinical symptoms, including attacks of syncope and convulsions.

- 2 Syncope and related manifestations result from one of the following three mechanisms: (a) cardiac slowing, (b) primary depression of the blood pressure or (c) a central reflex to the brain. The mechanism causing the reaction often appears in a mixed form.

- 3 Spontaneous attacks can be induced by mechanical stimulation of the carotid sinus.

- 4 Digitalis sensitizes the carotid sinus reflex mechanism. The routine preoperative administration of this drug, particularly to elderly patients, is not without danger.

- 5 Various morbid states play a rôle in sensitizing the carotid sinus reflex, and treatment of the disease, when efficacious, diminishes or abolishes the hypersensitive carotid sinus reaction.

- 6 Both the vagal and the depressor type of reaction can be controlled by ephedrine and epinephrine. Atropine abolishes the vagal type but has no effect on the depressor type. The cerebral type is not benefited by these drugs.

- 7 Surgical denervation of the carotid sinus abolishes spontaneous and induced attacks in suitable cases, but does not influence any of the unrelated accompanying symptoms.

# CAROTID SINUS NERVE IN MAN

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In spite of extensive experimentation with animals on the carotid sinus during the past decade, little is known of the function of this mechanism in man. The following cases are reported because they presented an opportunity to study the alterations in arterial tension which result in human beings when one carotid sinus is denervated.

It is not my purpose here to review the entire literature on the subject of the carotid sinus.<sup>1</sup> A brief statement of the known anatomic and physiologic facts will suffice. The carotid sinus is a small bulbous enlargement of the internal carotid artery at its point of origin from the common carotid artery. It receives (in the dog) a nerve from the superior cervical sympathetic ganglion, which is always present, and a small variable nerve which may arise from the vagus (Hering<sup>2</sup>). Some investigators have described a small branch from the hypoglossal nerve to the carotid sinus. However, it has been shown (Code and Dingle<sup>3</sup>) that the carotid sinus nerve, a branch of the glossopharyngeal nerve, is the only one of these nerves concerned in the carotid sinus reflex. It is now well established that increases in pressure within the carotid sinus are associated with a fall in general arterial tension, whereas a decrease in the pressure within the sinus results in an increase in general arterial tension, a diminished flow of blood in the extremities and an increase in flow of blood and of blood pressure in the brain (Bouckaert and Heymans<sup>4</sup>). The effect of the carotid sinus mechanism on respiration, cardiac rate and extrasystoles is not pertinent in this connection.

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Presented before the Chicago Society of Internal Medicine, Nov 25, 1935

From the Division of Neurology and Neurosurgery of the University of Chicago

1 Readers are referred to Ask-Upmark,<sup>8</sup> Weiss and Baker<sup>9</sup> and Bouckaert and Heymans<sup>4</sup> for a more complete bibliography

2 Hering, H E. Die Karotissinusreflexe auf Herz und Gefasse, Dresden, Theodor Steinkopff, 1927, Ueber die Wand des Sinus caroticus als Reizempfänger und den Sinusnerv als zentrípétal Bahn für die Sinusreflexe, Deutsche med Wchn-schr **51** 1140-1141, 1925

3 Code, C F, and Dingle, W T. The Carotid Sinus Nerve, Proc Staff Meet, Mayo Clin **10** 129-132, 1935. Code, C F, Dingle, W T, and Moorhouse, V H K. The Cardiovascular Carotid Sinus Reflex, Am J Physiol **115** 249-260, 1936

4 Bouckaert, J J, and Heymans, C. Carotid Sinus Reflexes. Influence of Central Blood-Pressure and Blood Supply on Respiratory and Vaso-Motor Centres, J Physiol **79** 49-66, 1933

In addition, Bronk and Stella<sup>5</sup> have shown that there is a rhythmic discharge of nervous impulses over the carotid sinus nerve as long as the pressure within the sinus is above 40 mm of mercury (in the rabbit) and that the rate of discharge is proportionate to the pressure—the higher the pressure the more rapid the discharge. The carotid sinus nerve is thus a depressor nerve which responds to pressure within the carotid sinus. The section of the carotid sinus nerve, therefore, interrupts a constant flow of depressor impulses to the vasomotor centers of the brain.

The possibility that section of one carotid sinus nerve (by section of the entire glossopharyngeal nerve) in man might give rise to some disturbance of the arterial tension was first drawn to my attention by the following case, in which the patient was operated on because of glossopharyngeal neuralgia. After the operation a marked rise in arterial tension occurred.

**CASE 1**—E. P., a school teacher aged 57, was referred to the University of Chicago Clinics by Dr. L. M. Robrock, of Michigan City, Ind. She was admitted on May 3, 1935, complaining of paroxysms of sharp, stabbing pain in the left side of the throat and radiating up into the left ear. The attacks were usually precipitated by swallowing and could be brought on by touching the left tonsillar fossa. The condition was of two years' duration. She had lost 25 pounds (11.3 Kg.) during the preceding year because of her inability to eat.

**Examination**—The blood pressure was 114 systolic and 72 diastolic. No abnormalities were found, except that paroxysms of pain could be elicited by touching the left tonsillar fossa.

**Operation**—On May 4, 1935, with the patient under the influence of tri-bromethanol in amylene hydrate and local anesthesia, with some ether, a left unilateral suboccipital craniectomy was performed, and the left ninth cranial nerve was sectioned.

**Blood Pressure**—After administration of the tri-bromethanol in amylene hydrate the blood pressure fell sharply, but it soon rose to 190 systolic and 120 diastolic (chart 1). The relationship of this hypertension to traction on the nerve or to section of it is not known. After the operation the blood pressure remained at a systolic level of 160 mm of mercury. On the following day the arterial tension reached a peak of 174 systolic and 90 diastolic, and on the second day there occurred a peak of 190 systolic and 80 diastolic. This systolic reading was 76 mm of mercury above the preoperative level. The tension continued to reach peaks of about 170 mm (systolic) for several days and then subsided to a level of 130 mm on the fourteenth postoperative day.

**Spinal Fluid Pressure**—Because of the arterial hypertension lumbar puncture was made on May 4 and on May 5, but the spinal fluid pressure on the two days was only 90 and 75 mm of fluid, respectively.

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<sup>5</sup> Bronk, D. W., and Stella, G. Afferent Impulses in the Carotid Sinus Nerve, *J. Cell & Comp. Physiol.* **1**: 113-130, 1932; The Response to Steady Pressures of Single End Organs in the Isolated Carotid Sinus, *Am. J. Physiol.* **110**: 708-714, 1935.



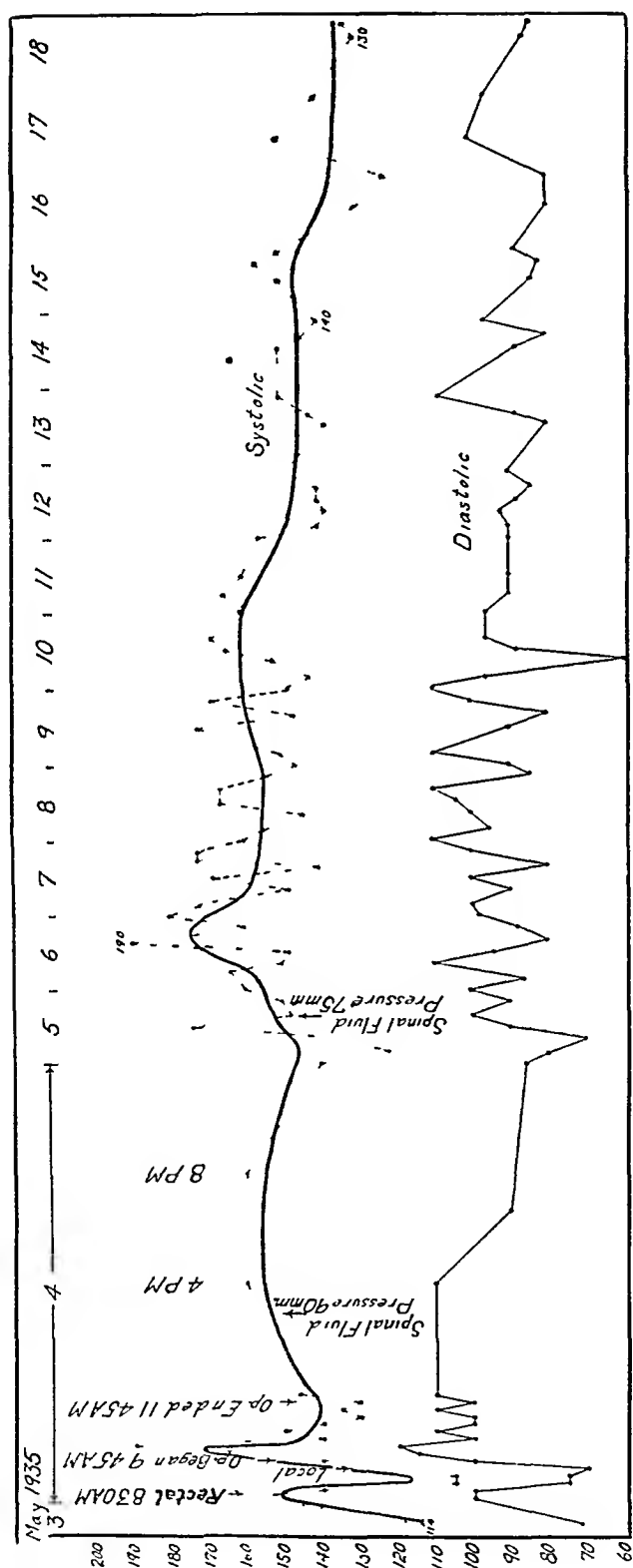


Chart 1 (case 1) —The blood pressure, systolic and diastolic, before, during and after section of the left glossopharyngeal nerve. In the upper tracing the broken line indicates the actual systolic readings, the upper solid line indicates the general trend of the systolic pressure. The lower line indicates the diastolic pressure. The changes on the day of operation, May 4, are shown in greater detail than those on the subsequent days. In this chart "rectal" indicates the time at which the injection of tri-bromethanol in amylene hydrate into the rectum was made, "local," the time when the scalp was infiltrated with a 1 per cent solution of procaine hydrochloride.

*Course*—The patient had no further pain, and she was discharged on May 19, fifteen days after the operation

*Comment*—It is obvious from the normal pressure of the spinal fluid that the arterial hypertension was not the result of increased intracranial pressure. As the patient was otherwise in good health, the only cause to which the high blood pressure could be attributed was section of the ninth nerve, of which the carotid sinus nerve is a branch. If this were the case, other patients in whom the ninth nerve had been sectioned should have shown the same phenomenon. Three other such sections had been performed in the clinics. The records were reviewed, and with one exception (case 4), which will be discussed later, all the patients did show a similar postoperative arterial hypertension. The histories follow

CASE 2—P. C.,<sup>6</sup> a housewife aged 36, was referred to the University of Chicago Clinics by Dr. Loren Avery, of Chicago. She was admitted on Jan. 20, 1930. On Sept. 8, 1924, while drinking coffee, she was seized suddenly with a severe knifelike pain in the left side of the throat. She was unable to swallow, had a choking sensation and then coughed. Subsequently she suffered from similar attacks about three times a day. These were usually brought on by drinking, swallowing, opening the mouth or coughing and occasionally seemed to appear spontaneously. The pain was always severe and knifelike. It involved the pharynx, the posterior part of the tongue, the posterior nasal region and the depth of the ear, all on the left side. A week after the onset perineorrhaphy was performed, and subsequently she was free from pain for one year. The attacks then returned and became more severe and more frequent. Various medications, eradication of foci of infection (?), injection of alcohol into the trigeminal nerve, intravenous injections and chiropractic treatments were tried without relief.

*Examination*—The results of examination were entirely negative except for slight hypesthesia of the lower part of the left side of the face, which was probably the result of the injection of alcohol into the fifth nerve. The blood pressure was 100 systolic and 64 diastolic.

*Operation and Course*—On Jan. 23, 1930, with the patient under ether anesthesia, a unilateral left suboccipital exposure was made. The left glossopharyngeal nerve was exposed and severed.

In the midst of the operation the systolic blood pressure suddenly rose from 95 to 115 mm. of mercury (chart 2). This was at about the time the nerve was interrupted, but the exact time relationship is unknown. At the close of the operation the blood pressure rose to 140 systolic and 80 diastolic.

At 6 and at 8 p. m. on January 24 the patient seemed in good condition. At 10 p. m. she was semicomatose, the blood pressure was 150 systolic and 80 diastolic. Respiration of the Cheyne-Stokes type soon appeared. She was taken to the operating room, the wound was explored, and an extradural blood clot was evacuated. She responded immediately and made an uneventful recovery, being discharged on February 8, sixteen days after the operation. At the time of writing she has suffered from no recurrence of the pain since the operation.

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<sup>6</sup> Previously reported by Percival Bailey (Neuralgias of the Cranial Nerves, *S. Clin. North America* 2: 61-77, 1931).

*Blood Pressure*—The systolic pressure before and during the first half of the operation ranged between 95 and 100 mm of mercury. After a sudden rise in the midst of the operation the blood pressure remained considerably above the pre-operative level, reaching as high as 148 systolic and 92 diastolic on the fourth postoperative day (not counting the peak caused by the hematoma), and returned to a systolic pressure of 110 only on the seventh postoperative day.

*Comment*—The condition in this case was complicated by the occurrence of a postoperative extradural hematoma which resulted in a sharp elevation in the arterial tension on the evening of the first postoperative day. However, this hemorrhage could not have explained the sharp rise in pressure during and immediately after the operation, and it is unlikely that it had anything to do with the prolonged hypertension which continued for a week after the operation, especially as the hematoma was evacuated and the patient showed no further signs of increased intracranial pressure or of medullary compression.

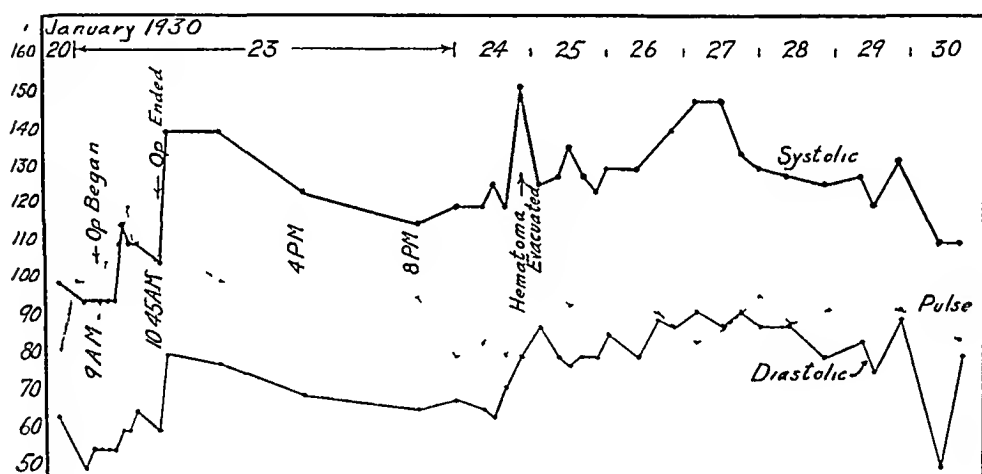


Chart 2 (case 2) —The systolic and diastolic blood pressures and pulse rate, before, during and after section of the left ninth cranial nerve. Ether anesthesia.

**CASE 3**—E O, a housewife aged 65, was referred to the University of Chicago Clinics by Dr T S F Johnson, of Joliet, Ill. She was first admitted on Sept 8, 1934, complaining of paroxysms of severe pain in the right side of the face, involving all three divisions of the trigeminal nerve, particularly the ophthalmic and the maxillary. This pain had been present for fifteen years and was growing more severe.

*Examination*—No abnormality was revealed other than the attacks of severe pain which were precipitated by talking or by touching the right cheek. The blood pressure was 160 systolic, 90 diastolic.

*Operation and Course*—The first operation was performed on Sept 11, 1934, with the patient under ether anesthesia. The posterior root of the right trigeminal nerve was sectioned. The approach was through the temporal fossa.

The blood pressure dropped to 110 mm of mercury, systolic, during the operation but subsequently varied little from the preoperative level (chart 3).

After the operation the patient was completely relieved from her pain and was discharged on September 19, eight days after the operation

*Second Admission*—On Nov 22, 1934, the patient again entered the clinics About the middle of October she had begun to have a feeling as though something were stuck in the region of the left tonsil, but she had no pain until November 1, when she was suddenly seized with a paroxysm of severe pain in the left side of the throat The attacks had recurred as frequently as ten to twelve times an hour from that time on The pain was confined to the left side of the throat and the tonsillar region, never radiating to the ear It was usually precipitated by swallowing

*Examination*—The blood pressure was 155 systolic and 90 diastolic Except for total anesthesia in the distribution of the right fifth nerve there were no abnormalities

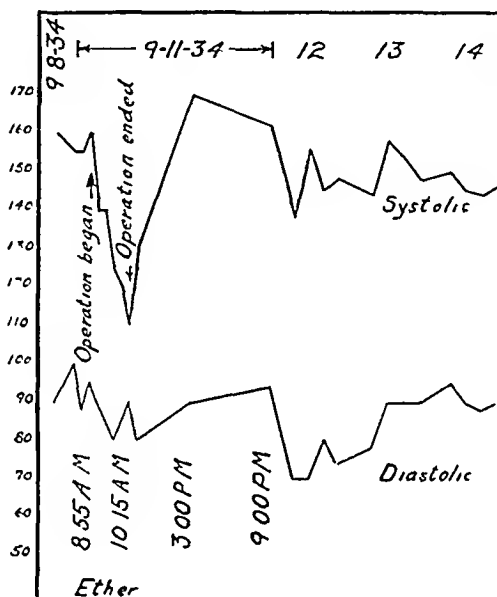


Chart 3 (case 3) —The blood pressure before, during and after section of the right trigeminal nerve by the temporal approach

*Operation*—The second operation was performed on Nov 24, 1934, with the patient under the influence of tri-bromethanol in amylene hydrate (90 mg per kilogram of body weight) and local anesthesia The cerebellum was elevated, and the left ninth cranial nerve was sectioned

*Blood Pressure*—A precipitous drop occurred after the administration of the anesthetic, but the blood pressure shortly returned to the preoperative level After the operation it rose to 190 systolic and 110 diastolic, and on the third postoperative day it reached 200 systolic and 110 diastolic It returned to the preoperative level about six days after the operation (chart 4)

*Lumbar Punctures*—On the first and the second postoperative days (November 25 and 26) lumbar puncture was made because of the arterial hypertension The spinal fluid pressure on the two days was 160 and 165 mm of fluid, respectively

The patient was discharged on Dec 3, 1934, eleven days after the operation and has had no further pain at the time of writing

*Comment*—This case is particularly interesting because of the association of trigeminal and glossopharyngeal neuralgia, an association which Peet<sup>7</sup> has found to occur frequently. As the trigeminal neuralgia was on the right and the glossopharyngeal neuralgia was on the left, there can be no question of the accuracy of the diagnoses. The absence of any rise in the arterial tension after the section of the fifth nerve as compared with the marked rise after the ninth nerve was sectioned leaves little reason to doubt that the arterial hypertension was the result of the interruption of the carotid sinus nerve.

CASE 4—A W, a man aged 39, was admitted on Aug 13, 1930, complaining of extreme dizziness, nausea, vomiting, headache, pain in the throat and ear on the left side, pain and swelling in front of the left ear, weakness of the left side of the face and impaired hearing in the left ear.

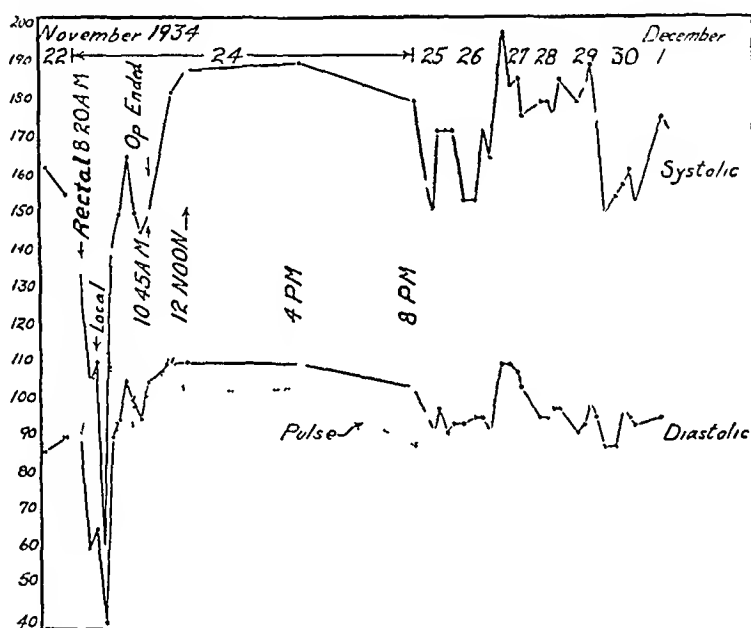


Chart 4 (case 3)—The blood pressure before, during and after section of the left glossopharyngeal nerve. In this chart "rectal" indicates the time at which the injection of tri-bromethanol in amylene hydrate into the rectum was made, "local," the time when the scalp was infiltrated with a 1 per cent solution of procaine hydrochloride.

The patient had first noted the swelling near the left ear in October 1929. It had gradually increased in size. The other symptoms had appeared in the course of the two months preceding admission.

*Examination*—A swollen indurated area was present below and in front of the left ear. There was paralysis of the left side of the face, partial deafness of the left ear of the middle ear type, hyperesthesia in the depth of the left external auditory meatus and hypesthesia in the area of distribution of the second and third cervical nerves on the left side.

A diagnosis of malignant neoplasm of the left side of the neck, with the involvement of various cranial and cervical nerves, was made. Section of the ninth cranial nerve was suggested, but the patient refused operation.

*Second Admission*—The patient was readmitted to the hospital on Sept 9, 1930. The mass in the left side of the neck had increased in size, and the pain, chiefly deep in the left ear and also in the left side of the throat, had increased greatly in severity. He also complained constantly of dizziness.

Examination revealed no change except an increase in the size of the tumor.

*Operation*—On Sept 17, 1930, operation was performed with the area under local anesthesia. Through a unilateral suboccipital exposure the cerebellum was retracted medially, and the seventh, eighth and ninth cranial nerves on the left side were sectioned. The patient still complained of pain in the base of the tongue, and pain in that region could be elicited by touching the tenth nerve. The uppermost fibers of the tenth nerve were then sectioned. After the operation he was hoarse and for a time was unable to swallow. Some pain in the neck persisted.

*Blood Pressure*—The blood pressure fluctuated considerably during the operation. It was followed for two days only, but no elevation from the preoperative level was observed during that time (chart 5).

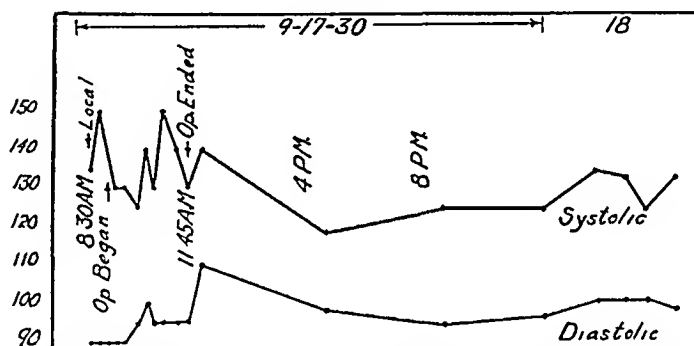


Chart 5 (case 4)—The blood pressure during and after section of the left seventh, eighth, ninth and part of the tenth cranial nerves.

*Comment*—This was the only one of the four cases in which the ninth cranial nerve was sectioned in which a postoperative rise in blood pressure did not occur. It is believed that in this case the tumor had probably invaded and destroyed the carotid sinus nerve prior to the operation.

After having this phenomenon drawn to my attention by case 1 and its occurrence confirmed by cases 2 and 3, I was fortunate in having the opportunity to section the ninth nerve on the right side (all the previous ones had been on the left side) in a patient suffering from glossopharyngeal neuralgia. More careful observations during the operation were possible in this instance than in the preceding cases.

*CASE 5*—N. L., a clerk 40 years of age, was first seen in the neurologic outpatient department of the University of Chicago Clinics on Feb 17, 1934. He complained of paroxysmal attacks of pain in the posterior part of the tongue and in the throat, which were brought on by swallowing and by talking. The pain did

not radiate into the ear. He stated that he also had a dull, more continuous pain in the right temple and at times in the right side of the face. The pain was always absent during the summer months. Because of the atypical nature of the condition he was kept under observation for a time.

The patient returned on Oct 23, 1935. The pain had not been relieved during the summer, and he had decided to have the operation. In order to confirm the diagnosis Dr J R Lindsay anesthetized the throat with cocaine. This completely relieved the pain.

*Examination*—The general physical and neurologic examinations gave negative results. The blood pressure was repeatedly determined on both arms and was found to vary between 108 systolic and 65 diastolic and 112 systolic and 65 diastolic. The diagnosis was glossopharyngeal neuralgia on the right side.

*Operation*—On Nov 2, 1935, with the patient under ether anesthesia, a sub-occipital exposure was made on the right side, the cerebellar hemisphere was elevated, and the glossopharyngeal nerve was severed.

The patient made an uneventful recovery and was discharged a week later, on Nov 9, 1935.

*Blood Pressure*—During the first part of the operation, while the exposure was being made, the blood pressure varied between 90 and 120 mm of mercury systolic, and between 50 and 75 mm diastolic. During this period the blood pressure was determined at five minute intervals. After the nerve was cut, it was determined at one minute intervals. At the time of sectioning of the nerve the systolic pressure fell slightly, and the diastolic pressure fell from 60 to 40 mm. Shortly thereafter the blood pressure began to rise steadily, and in seven minutes it reached a peak of 186 mm systolic and 80 mm diastolic (chart 6 B). It then fell to the preoperative level only to rise to a second peak of 162 systolic and 72 diastolic and then subside to 106 systolic and 58 diastolic at the close of the operation. Very soon after the operation it rose again and continued between 130 and 145 systolic and between 72 and 100 diastolic for the remainder of the patient's stay in the hospital. When he was seen on Nov 13, 1935, eleven days after the operation, the blood pressure was 132 systolic and 70 diastolic (chart 6 A).

*Cardiac and Respiratory Rate*—It was not feasible to determine these as frequently during the operation as the blood pressure was measured. However, the observations which were made indicated a rise in both the cardiac and the respiratory rate immediately after the nerve was severed. During the following days the respiratory rate remained normal, and nothing definite could be stated concerning the cardiac rate. The pulse was definitely more rapid, but this may have had no significance, as the patient ran a slight febrile course.

This case is particularly interesting in that it shows the immediate marked rise in systolic blood pressure which occurs soon after the glossopharyngeal nerve is severed and the secondary rise which appears several hours later and is most marked on the second or third postoperative day. It is to be anticipated that the blood pressure in this case, as in the others, will soon return to normal, although a sufficiently long period of observation has not occurred at the time of writing to determine this point.

Although the absence of any rise in blood pressure after section of the fifth nerve in case 3 offered a fair control of these observations, it

was thought advisable to review another group of cases in which the surgical approach was much the same as that for glossopharyngeal neuralgia but in which the ninth nerve was not disturbed. Reports follow of two cases typical of this group.

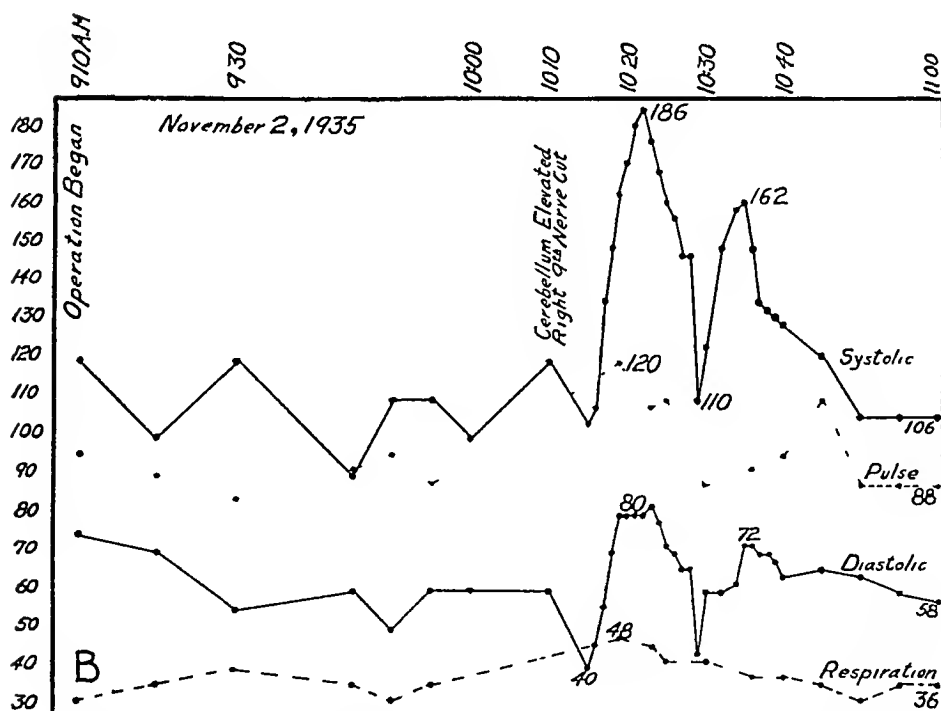
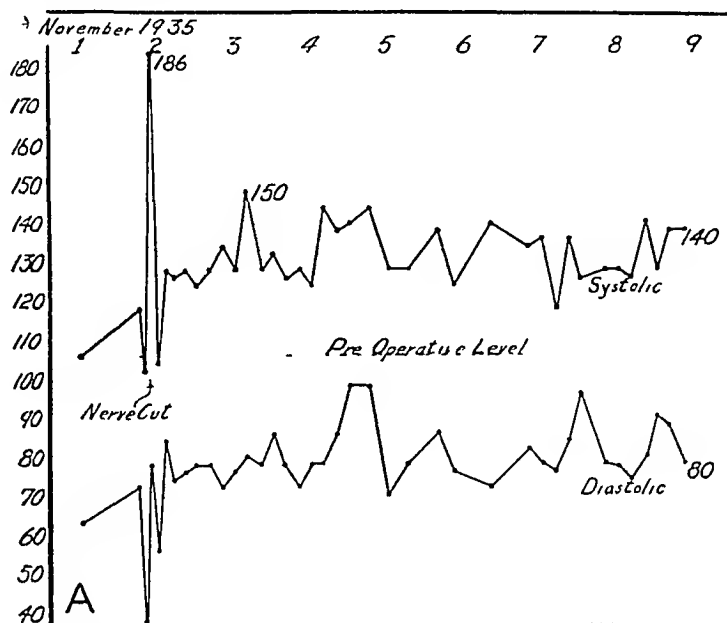


Chart 6 (case 5)—*A*, the elevation in blood pressure resulting from section of the right glossopharyngeal nerve. *B*, a more detailed graph of blood pressure, pulse and respiration during the operation. Determinations were made by Dr Harold Koch. Ether anesthesia.

CASE 6—L. R.,<sup>6</sup> a carpenter aged 59, was referred to the University of Chicago Clinics by Dr George B. Hassin, of Chicago. He had suffered for twelve years



from typical trigeminal neuralgia, which involved the entire right side of the face. Because of a gross anatomic anomaly of the floor of the temporal fossa, previous operations had been confined to section of the peripheral divisions of the nerve and had given only temporary relief. A section of the fifth nerve by the suboccipital approach (Dandy) was therefore decided on.

*Examination*—No abnormalities were revealed except an absence of sensation over the greater part of the face on the right side. The blood pressure was 140 systolic and 50 diastolic.

*Operation and Course*—On March 7, 1930, operation was performed with the patient under ether anesthesia. Unilateral suboccipital incision and craniectomy were done. The cerebellum was retracted medially until the fifth nerve was exposed. It was divided by a hooked knife, and the wound was closed.

The postoperative course was uneventful, and the patient was discharged twelve days after the operation.

*Blood Pressure*—Variations in blood pressure during the operation were not unusual. The blood pressure was followed for two days after the operation and was found to remain at the preoperative level (chart 7).

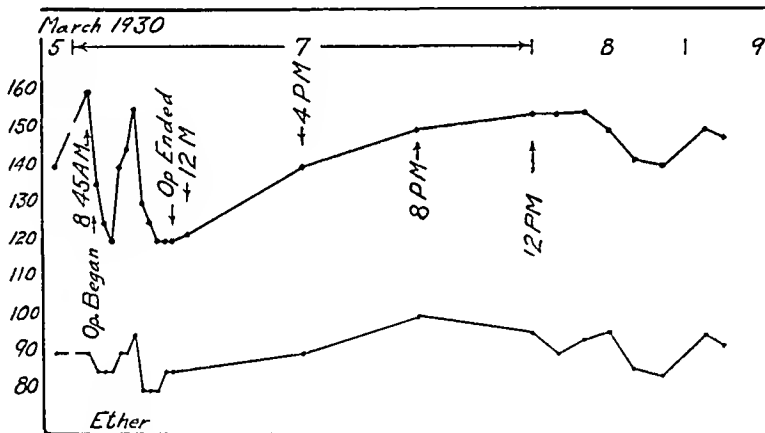


Chart 7 (case 6) —The effect on the blood pressure of section of the right fifth cranial nerve by the suboccipital approach. Ether anesthesia.

*Comment*—The operative procedure necessary to expose and section the fifth nerve by the suboccipital approach differs little from that used in sectioning the ninth nerve. This case illustrates clearly that the operative procedure necessary for exposure of the nerve is not the cause of the hypertension and leaves little doubt that section of the ninth nerve is directly responsible.

**CASE 7**—E. N., a housewife aged 65, was referred to the University of Chicago Clinics by Dr. Peter Bassoe, of Chicago, and was admitted on Dec. 13, 1929. She had suffered from paroxysms of pain in the left side of the face for eighteen years. Seven years previously a partial retrogasserian neurectomy had been performed at another hospital, with only temporary relief. Two years later the wound was reexplored, and the section of the nerve was completed. Again the pain was relieved for a short time.

*Examination*—Enophthalmos on the left and ptosis of the left upper eyelid were noted. The left pupil did not react to light. Ocular movements were normal. There was partial weakness of the left side of the face.

The blood pressure was 215 systolic and 95 diastolic. The heart was enlarged, and occasional extrasystoles were present. The patient gave a history of occasional attacks of precordial pain. There was a moderate degree of peripheral arteriosclerosis.

The patient was placed under the care of a cardiologist for a time.

*Operation and Course*—On March 18, 1930, operation was performed with the patient under ether anesthesia. The blood pressure was 180 systolic and 85 diastolic. The usual unilateral suboccipital exposure was made. The cerebellum was retracted medially, and a small meningioma was removed from the left side of the pons.

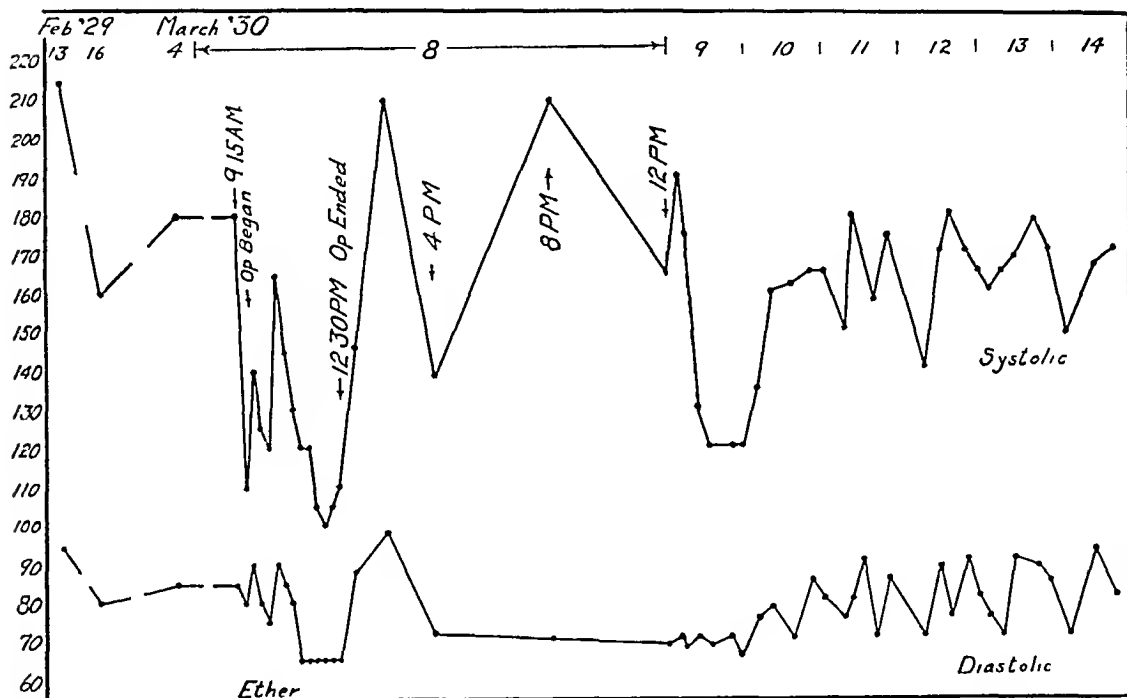


Chart 8 (case 7)—The blood pressure as affected by the removal of a small meningioma from the right side of the pons by a suboccipital approach. Ether anesthesia.

After the operation the patient was completely relieved of pain and remained so. The weakness of the left side of the face was more marked for a time, and a corneal ulcer developed, which soon healed.

*Blood Pressure*—During the operation the blood pressure was considerably below the preoperative level (chart 8). After the operation, except for two occasions during the afternoon of the day of operation when the systolic pressure reached 210 and one on the following morning when it reached 190, the blood pressure remained at or below the preoperative level of 180.

*Comment*—The condition was complicated by cardiovascular disease, but the results in this case as well as those in case 6 show that the sub-

occipital approach to the nerves in the posterior cranial fossa is not responsible for the postoperative hypertension observed after section of the ninth cranial nerve

#### REVIEW OF THE LITERATURE

An extensive review of the literature dealing with glossopharyngeal neuralgia reveals no observations on the blood pressure after section of the glossopharyngeal nerve, with the exception of those in the cases briefly mentioned in the excellent monograph by Ask-Upmark.<sup>8</sup> In the first of these cases a sharp rise of arterial tension (systolic), of from 100 to 175 mm of mercury, occurred when the right ninth cranial nerve was cut, in the second a momentary drop in blood pressure occurred, and in the third a temporary but sharp rise was noted. In no instance were prolonged observations made. Weiss and Baker<sup>9</sup> reported one case (possibly the same as Ask-Upmark's case 1) in which section of the right glossopharyngeal nerve intracranially was followed by an immediate sharp rise in arterial tension. They reported another interesting case in which a patient suffering from fainting attacks was found to have a tumor of the right carotid sinus. Pressure on the tumor reproduced the attacks. The patient was operated on, the tumor was removed, and the carotid sinus was denervated. There occurred an immediate sharp rise in the blood pressure, which increased to a peak of 225 systolic and 120 diastolic from a preoperative pressure of 160 systolic and 100 diastolic. The increase in the arterial tension persisted for thirty-six hours after the operation. Budde<sup>10</sup> reported a case in which section of the nerve of the sinus resulted in an immediate moderate rise in blood pressure. Leriche, Fontaine and Froehlich<sup>11</sup> reported seven instances of denervation of the carotid sinus. Both sinuses were denervated in five cases and one in two cases. Immediately after denervation they noted a marked rise in arterial tension, which subsided in a few days, the tension becoming normal. No effect on the cardiac rhythm or the respiratory rate was observed.

Bevan and McCarthy<sup>12</sup> in reporting a case of tumor of the carotid body and reviewing the reports of 142 other cases referred to reports

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8 Ask-Upmark, E. The Carotid Sinus and the Cerebral Circulation. Anatomical, Experimental and Clinical Investigation, Including Some Observations on the Rete Mirabile Caroticum, *Acta psychiat et neurol*, supp 6, 1935, pp 1-374.

9 Weiss, S, and Baker, J. P. The Carotid Sinus Reflexes in Health and Disease, *Medicine* **12** 297-354, 1933.

10 Budde, M. Chirurgische Erfahrungen über den Carotissinusdruckversuch, *Ztschr f d ges exper Med* **50** 207-211, 1926.

11 Leriche, R, Fontaine, R, and Froehlich, F. L'enervation sinu-carotidienne, *Presse méd* **43** 1217-1220, 1935.

12 Bevan, A. D, and McCarthy, E. R. Tumors of the Carotid Body, *Surg, Gynec & Obst* **49** 764-779, 1929.

of fainting attacks and attacks of "Stokes-Adams syndrome" precipitated by pressure on the tumor but made no mention of alterations in blood pressure in association either with the tumor or with operation on it Rankin and Wellbrock<sup>13</sup> in another report of such tumors referred to attacks of fainting elicited by pressure on the tumor but made no reference to arterial tension

Dorrance,<sup>14</sup> discussing ligation of the vessels of the neck, stated that ligation of the common carotid artery results in a reduction of the pressure in the carotid sinus and that this in turn may result in extrasystoles and even fibrillation He made no reference to any rise in blood pressure caused by this procedure

Except for the fact that pressure over the carotid sinus will induce a fall in blood pressure and a slowing of the cardiac rate (see Weiss and Baker<sup>9</sup> for a fuller discussion) few observations have been made concerning the carotid sinus mechanism in man

#### COMMENT

In view of the changes in blood pressure observed in the cases reported here and in the few instances cited from the literature, there can be little doubt that the section of one carotid sinus nerve or of one glossopharyngeal nerve results in a temporary rise in arterial tension That the rise is only temporary, persisting for from five to twelve days in our cases, is not surprising, since several investigators (Green, De Groat and McDonald,<sup>15</sup> Green and De Groat,<sup>16</sup> Koch and Mattonet<sup>17</sup> and others) have found experimentally that even after section of both carotid sinus nerves and of both aortic depressor nerves the resultant rise in blood pressure is not permanent, at least it is not maintained nearly at the initial high level

The explanation of the hypertension which ensues after section of a carotid sinus nerve seems simple Bronk and Stella<sup>5</sup> demonstrated a constant flow of nervous impulses over the carotid sinus nerve Their

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13 Rankin, F W, and Wellbrock, W L A Tumors of the Carotid Body, *Ann Surg* **93** 801-810, 1931

14 Dorrance, G M Ligation of the Great Vessels of the Neck, *Ann Surg* **99** 721-742, 1934

15 Green, M F, De Groat, A F, and McDonald, C H Observations on Denervation of the Carotid Sinus and Section of the Depressor Nerves as a Method of Producing Arterial Hypertension, *Am J Physiol* **110** 513-520, 1935

16 Green, M F, and De Groat, A F Observations on the Late Effects of Denervation of the Carotid Sinuses and Section of Depressor Nerves, *Am J Physiol* **112** 488-492, 1935

17 Koch, E, and Mattonet, K Versuche zur Frage der arteriellen Hypertonie nach Dauerausschaltung von pressoreceptorischen Kreislaufnerven, *Ztschr f d ges exper Med* **94** 105-113 1934

rate is proportionate to the pressure within the sinus. These impulses have a depressor action. When they are abolished, the pressure rises as a result. The rise, however, is temporary because the other cardiovascular regulatory mechanisms soon gain control.

It would appear from these cases that section of either the right or the left carotid sinus nerve will give the same results in man. In these cases no significant changes in pulse rate or respiratory rate were observed unless it was in case 5 immediately after the section of the nerve.

#### SUMMARY

Four cases of glossopharyngeal neuralgia treated by intracranial section of the glossopharyngeal nerve are reported. In each instance a marked rise in blood pressure occurred after the operation and lasted several days. This is interpreted as due to interruption of the carotid sinus nerve, a branch of the glossopharyngeal nerve.

A case in which a malignant neoplasm of the neck was treated by intracranial section of the seventh, eighth, ninth and part of the tenth cranial nerves is reported, no rise in blood pressure occurred, probably because of involvement of the carotid sinus nerve by the tumor.

Two cases are reported in which a similar surgical approach was used, but the ninth cranial nerve was not sectioned. No rise in blood pressure occurred.

The very limited pertinent literature is reviewed.

The conclusion is drawn that in man the section of one carotid sinus nerve or of the glossopharyngeal nerve of which it is a branch results in a rise in arterial tension of a few days' duration.

# ADRENAL SYMPATHETIC SYNDROME WITH UNUSUAL VARIATIONS IN CARDIAC RHYTHM

REPORT OF A CASE

ALEX M BURGESS, M D

GEORGE W WATERMAN, M D

AND

F B CUTTS, M D

PROVIDENCE, R I

Within the last few years a great deal of attention has been given to the relation of the adrenal glands to arterial hypertension. Both hyperplasia and tumor of these organs have been found in some instances to be associated with high blood pressure. In particular, a small number of instances of tumor arising from the chromaffin tissue of the adrenal medulla have been reported as characterized by an unusual clinical picture, the most striking feature of which is paroxysmal hypertension. It is the purpose of this communication to report an instance of this condition, including certain observations on the heart which are of interest.

Among the published reports of instances of this type of adrenal tumor there have been several excellent descriptions of the associated clinical picture, of which condition our patient presented an extreme example. This symptom complex has been called the "suprarenal sympathetic syndrome" by Belt and Powell<sup>1</sup> "in contradistinction," as they put it, "to the 'suprarenal genital syndrome' which is associated with certain neoplasms of the cortical portions of these glands." It is characterized by paroxysmal attacks of hypertension, with tachycardia, pallor and nausea and at times vomiting and by a feeling of great tension, often with cyanosis and choking and sometimes with pulmonary edema. These authors have recently published, with the report of a complete study of a typical case, an excellent survey of the literature, including a review of twenty-three reported cases in which the clinical manifestations may be considered definitely as characteristic of the condition.

At about the same time Coller, Field and Durant<sup>2</sup> reported a striking case of a youth of 16 in which operation was followed by an apparently

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1 Belt, A E, and Powell, T O. Clinical Manifestations of the Chromaffin Cell Tumors Arising from the Suprarenal Medulla, Surg, Gynec & Obst **59** 9 (July) 1934

2 Coller, F A, Field, H, Jr, and Durant, T M. Chromaffin Cell Tumor Causing Paroxysmal Hypertension, Relieved by Operation, Arch Surg **28** 1136 (June) 1934

complete recovery To these may be added the recent description of three additional instances of the condition by Pincoffs,<sup>3</sup> in one of which the tumor was found in the median line, apparently arising from a chromaffin cell rest in a prevertebral sympathetic ganglion Such rests of pheochromocytes are known to occur normally in these ganglions, and tumors arising from them have been given the name paraganglioma, which, in our opinion, is an undesirable term, as it is based merely on the location of the tumors whereas the term pheochromocytoma indicates the type of cell and should, we believe, be applied to these neoplasms, whether they arise from the medulla of the adrenal glands or from rests of chromaffin cells elsewhere

#### REPORT OF CASE

R N, a 25 year old Jewish housewife, consulted one of us on April 20, 1933 At that time she complained of attacks of palpitation, which she described as "thumping" in the chest They occurred usually during the night and began two years before examination, after the sudden death of her father The attacks lasted five or ten minutes and were associated with pallor and gagging but no vomiting There was never loss of consciousness As a rule the attacks awakened the patient in the night, but occasionally one occurred during the day She stated that they made her throat "expand and the vessels stand out" and that although the action of the heart was forceful and uncomfortable, the rate was not accelerated There had been no dyspnea on exertion The patient had consulted many doctors without relief Rentgenologic study of the gastro-intestinal tract suggested appendicitis, but appendectomy performed in April 1932 was not followed by any improvement Tonsillectomy was performed in May 1932

*History*—A brief summary of the relevant facts reported in the record shows that the patient had measles, pertussis and scarlet fever in childhood At the age of 6 years she had pneumonia followed by empyema, which was drained Menstruation began at the age of 14 and always occurred from six days to three weeks late She usually had flow for two days and sufficient discharge to stain a napkin for four days and had occasional cramps A review of the function of the various systems gave essentially negative results, except that a constant tendency to constipation was noted Her average weight was 105 pounds (47.5 Kg), and she said she had lost 5 pounds (2.3 Kg) during the previous five weeks

*Marital and Family History*—The patient had been married a year and a half, and no pregnancy had occurred The family history was negative as regards benign or malignant tumor or other diseases relevant to her problem In particular, there was no record of attacks similar to hers

*Physical Examination and Course*—The patient was 61½ inches (159.2 cm) tall (with shoes) and weighed 101½ pounds (46.03 Kg) clothed The temperature was 98.3 F and the pulse rate was 72 The blood pressure was 118 systolic and 76 diastolic

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<sup>3</sup> Pincoffs, M C Medullary Tumors of the Adrenal Glands, read at the nineteenth annual clinical session of the American College of Physicians, Philadelphia, April 30, 1935, to be published

The physical examination in general gave negative results. The heart was apparently not enlarged, its rate and rhythm were normal, and no murmurs were heard. The reaction to exercise was considered normal. The urine was normal. A summary of the facts elicited in the examination at that time led to a tentative diagnosis of cardiac neurosis, although it was noted that the attacks were unusual and their origin obscure. The patient was advised to report attacks promptly in the hope that one might be observed, and she was placed temporarily on a regimen of partial rest and advised to take phenobarbital,  $\frac{1}{4}$  grain (0.0162 Gm) three times daily and  $\frac{1}{2}$  grain (0.0324 Gm) at bedtime. It was suggested that she see a neuropsychiatrist.

A report from Dr. Kramer showed the basal metabolic rate to have been —14.6 per cent a few weeks before the examination.

The patient was seen again on May 15 and on June 8. On the latter date she had just recovered from an attack which occurred while she was shopping, but nothing abnormal could be found. The color was good, the heart was apparently normal, and the blood pressure was 104 systolic and 70 diastolic.

After that the patient did not report further and consulted other physicians, both in Providence and in New York. Finally, as had been suggested to her, she called on a neuropsychiatrist, Dr. Charles A. McDonald. He elicited the same history as to attacks, except that at that time she stated that they usually lasted twenty minutes and were at times associated with headache of a "binding" nature. He wrote as follows: "I saw her several times until she became pregnant, and on Oct. 27, 1934, when she told me about her pregnancy she said that since becoming pregnant she had stopped vomiting, retching and expectorating. The next and last time I saw her was on Jan. 22, 1935. She was in the hospital suffering from what I then called a vasovagal spell, and I noted that the attack was like the type she had had before, but much worse."

The patient was next seen, by another of us, on Oct. 25, 1934, having been referred by Dr. McDonald for care of her pregnancy. Her last menstrual period had occurred on Sept. 1, 1934. The history obtained at that time was similar to that elicited before, except that after the onset of pregnancy the attacks had diminished greatly in frequency and severity and had been practically absent for four weeks. The result of physical examination in general was essentially as noted before.

The weight (clothed) was 104 $\frac{3}{4}$  pounds (47.51 Kg), the blood pressure, 115 systolic and 70 diastolic and the pulse rate, 72. The urine was normal.

On Nov. 23, 1934, the patient reported several attacks of palpitation, nausea and vomiting, such as she had had before she became pregnant. The blood pressure was 120 systolic and 80 diastolic. The weight was 106 $\frac{3}{4}$  pounds (47.96 Kg). The urine was normal.

On Dec. 18, 1934, the blood pressure was 120 systolic and 80 diastolic. The weight was 108 $\frac{1}{4}$  pounds (49.1 Kg). The patient stated that she felt very well as far as her pregnancy was concerned but that she still had attacks as before, not relieved by vomiting. Her general condition seemed excellent.

On Jan. 18, 1935, the patient said that she was not so nauseated as previously and distinguished between what she called her "pregnancy nausea," which was "easy" and did not trouble her in the least, and her "old" nausea, which was accompanied by gagging, palpitation and headache. She also complained that she felt a lump in her abdomen, which became very hard when an attack occurred. Examination showed nothing unusual except a pregnant uterus. No other mass was found. Urinalysis gave negative results.



The following is quoted from the office record of Jan 21, 1935 "The patient's sister called by telephone this afternoon at 3 00 to say that Mrs N had been vomiting all day, was most distressed and was vomiting blood On my arrival, as I walked into her room, she was leaning over the edge of her bed, her skin was dusky bluish gray, and frothy pink serum was coming out of her mouth into a basin on the floor She was coughing and gagging Her pulse rate was about 144, and the beat was regular The paroxysm lasted about two minutes after my arrival, and then she sank back exhausted Her color gradually became better, and her strength returned Suddenly she looked very anxious and said 'Now it's coming again,' and put her hand to her precordium I listened, and her heart had taken on a strong, full, irregular beat, the rate being about 50 but with extrasystoles, or skipped beats She complained of severe binding headache and then of a lump rising in her abdomen, which examination showed to be the uterus, which contracted and raised itself as if in the second stage of labor, except that there was no pain or bearing down After that she became faint, and severe nausea, vomiting and gagging occurred She was very cyanotic, and as I listened over the precordium, the cardiac rhythm changed, becoming rapid and regular At the same time moist râles appeared, and bloody frothy serum typical of pulmonary edema was coughed or vomited Gradually the violence of the attack subsided, and the patient sank back exhausted Episodes such as have been described occurred every three to five minutes She was transferred to a hospital, where sedatives (morphine and chloral hydrate) seemed to quiet her, and the attacks stopped She stayed in the hospital for one week As she had no more attacks she was allowed to go home, the pulse rate and the blood pressure being normal For several days after her admission to the hospital her pulse was rapid and there were moist rales in the chest and a murmur over the first and second left interspaces near the sternum"

On Feb 12, 1935, the report in the office record was "The patient had a similar series of episodes at home today, eventually controlled by morphine, scopolamine and atropine, although it seemed as if she was going to die of pulmonary edema in one attack"

When the patient was seen in the office on Feb 22, 1935, she seemed normal in every way The weight was 114¾ pounds (52 Kg) When she was seen on March 4, 1935, she was having a slight attack In this attack, as in others observed later, there were cyanosis, pallor, marked uterine contraction, nausea and vomiting The attacks continued with intervals of several days' freedom up to the time of her delivery on March 29 The child was premature and died after several hours

Treatment of various sorts were tried—ordinary sedatives (pentobarbital, morphine and scopolamine), epinephrine, atropine and quinidine—without definite effect It is worthy of note that at the time of delivery the patient did not suffer from an attack, although such attacks did occur about twenty-four hours later Figure 1 illustrates the changes in blood pressure noted in an attack on March 30

As the attacks varied greatly in their intensity and frequency, it is perhaps best to describe a typical and severe example, such as occurred on April 6 When seen the patient showed a heart rate of from 120 to 140, with a regular rhythm and a loud systolic murmur audible to the left of the sternum in the second and third spaces The color was good, and she was relaxed and drowsy The blood pressure was 65 systolic and 40 diastolic After a few minutes the systolic pressure was noted to be 100, and the sounds were distinctly louder, increasing in loudness during the next ten or twelve beats in a striking crescendo As the sounds became very loud, the rate became slower, and then distinctly irregular

The blood pressure at that time was 240 systolic and 180 diastolic. After a few seconds the rhythm again became regular, and a gallop rhythm developed. Absence of the systolic murmur was noted. Repeated observations of blood pressure showed a gradual fall during the next ten minutes, with a disappearance of the gallop rhythm and a reappearance of the murmur when the systolic pressure reached about 120. The fall in pressure continued until the original level, approximately 60 systolic and 45 diastolic, had been reached. This whole cycle was repeated every fifteen minutes throughout the early part of the day. Later the intervals between attacks became much longer. With the onset of the slow strong beats and the rise in pressure, the patient became pallid and then cyanotic and complained of fulness in the head and the throat and then of nausea. She vomited in many of the attacks and in some coughed up a pinkish, frothy fluid and showed moist râles in the lungs. The severity of the attacks was mitigated somewhat by sedatives. Electrocardiographic studies were made throughout the entire cycle.

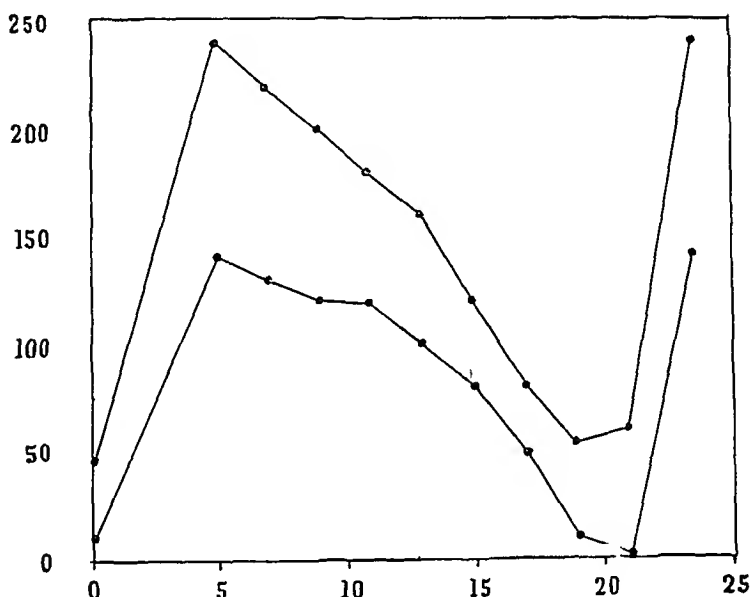


Fig 1—Serial observations of blood pressure during an attack on March 30. The upper line indicates systolic pressures, the lower line, diastolic pressures, in millimeters of mercury. Time is given in minutes.

and were correlated with symptoms and with changes of blood pressure. These are discussed later in this paper.

As the patient's puerperium was otherwise normal, she was removed on the tenth day post partum to the Jane Brown Memorial Hospital. Retrograde pyelograms showed a marked displacement downward and compression of the upper part of the right kidney, and a tentative diagnosis of pheochromocytoma of the right adrenal gland was made.

Roentgen treatment was carried out by Dr. Batchelder, eleven treatments being given, but by May 6 recurrent attacks with pulmonary edema had become so alarming that operation was decided on.

Laboratory studies on March 8, 1935, showed the dextrose content of blood to be 125 mg per hundred cubic centimeters (fasting), the nonprotein nitrogen content 31 mg and the carbon dioxide-combining power 53 volumes per cent. On March 25, 1935, the dextrose content of the blood was 110 mg per hundred cubic

centimeters (fasting), and nonprotein nitrogen 29 mg. Slight glycosuria was observed thereafter on several occasions. The Wassermann reaction of the blood was negative.

*Operation*—On May 8, 1935, operation, requiring one hour, was performed, with the patient under preliminary anesthesia with phenobarbital and morphine sulfate and later nitrous oxide with oxygen. *Technic*. An upper right rectus incision was made. When the peritoneum was opened, the liver was found pushed down below the level of the umbilicus by a tumor of the adrenal gland, which was about 10 cm. in diameter. To give better exposure beneath the surface of the liver, a horizontal incision was made from about the midpoint of the longitudinal incision, opening the flank to the midmaxillary line. The liver was then reflected, and the tumor was exposed retroperitoneally and above the kidney. The peritoneum



Fig 2—Pyelogram showing displacement of the right kidney downward and outward.

was incised longitudinally, and the tumor was shelled out, a definite line of cleavage being established. The tumor was removed without difficulty and with little bleeding. The walls of the bed of the tumor were brought together by a purse-string suture, and the peritoneum was closed with a continuous suture. The abdominal wall was closed in layers.

The patient's condition previous to the operation was poor. Immediately after the anesthetic began to be administered, there was a marked drop in the blood pressure, the pulse was very rapid, but the respiratory rate was not increased and the patient was warm. It was the consensus that the operation should proceed. There was practically no change in the condition during the operation. The pulse was rapid and the blood pressure could not be obtained throughout.

After the operation the patient was transferred to her room. Small doses of epinephrine were given every fifteen minutes. The blood pressure still did not

rise. She was rather cyanotic but was warm. She was given inhalations of carbon dioxide and oxygen at intervals. After two and one-half hours, as she had not seemed to react and as her extremities were cold, an intravenous infusion of a 5 per cent solution of dextrose was decided on. The pulse rate began to improve immediately. Her color became better. She regained sufficient consciousness to complain of pain in her right side, for which she was given  $\frac{1}{6}$  grain (0.0108 Gm) of morphine sulfate. Just as the intravenous infusion was being finished, she had a sudden attack of pulmonary edema, her lungs filled completely with fluid, and she appeared to drown in her own secretions. Artificial respiration was given, and large quantities of fluid poured out of her mouth, but respiration could not be reestablished, and she was soon dead.

*Pathologic Report*—The pathologic examination of the tumor was made by Dr. B. Earle Clarke.

**Macroscopic Examination** The specimen consisted of a spherical tumor which measured 9 cm in diameter. It was covered by a thin fibrous capsule. There were fibrous tags which roughened the surface, but at no place was the capsule broken. From one side there was a flat shelflike projection, which left the surface at an acute angle, so that it tended to parallel the adjacent capsular surface. At its attachment this measured 5 cm in length. It projected outward 1 cm and was 3 mm in thickness. When cut across it presented two layers of yellow cortex enclosing a brownish medulla typical of the normal adrenal gland. The capsule of the tumor was continuous with the capsule of this portion of the adrenal gland, and the glandular tissue became lost in the tumor. In three other places irregular plaques of thinned-out yellow adrenal cortex could be seen through the capsule. The tumor mass was rather soft and dark red.

On section, an eccentrically placed cyst measuring 6 cm in diameter was noted. This cyst had a thick, dense, fibrous capsule. The lining was smooth and shiny. It was filled with soft, brown granular and amorphous material. There were also smaller cavities, which lacked the thick wall and contained clotted and fluid blood. The solid parts remaining between these cysts were soft, red and hemorrhagic.

**Microscopic Examination** The sections were fixed with Zenker's fluid and stained with hematoxylin and eosin. In two sections thin layers of compressed normal adrenal cortex were present on the surface. No normal medulla was demonstrable between this cortical tissue and the tumor. The tumor was vascular. There were numerous small blood-filled spaces, with only endothelial walls. In addition, there were many larger, irregular spaces which had no endothelial lining and were, no doubt, hemorrhagic cysts resulting from necrosis. There was also considerable hemorrhage into the solid parts.

The cells of the tumor varied greatly in size and shape. In general they were large. In places they tended to be spindle-shaped and to form whorls, but for the most part they were solidly massed. There was no tendency to form acini. These cells had an abundance of finely granular cytoplasm. The cell outlines were indistinct and frequently blended to form a syncytium. There were cytoplasmic prolongations. Vacuoles and irregular areas of hyaline degeneration were occasionally noted. I was unable to identify specific hyaline inclusion bodies, such as have frequently been described in such tumors.

The nuclei, too, varied greatly. They were vesicular, and many contained a distinct nucleolus. Frequently they were ovoid or spindle-shaped. Occasionally three or more large nuclei were heaped together, forming a sort of multinucleated giant cell. More frequently there were seen single gigantic nuclei of bizarre shape. No mitotic figures were present.

The stroma was scanty.

Small blocks of the tissue were placed overnight in a 10 per cent solution of potassium di-chromate. Frozen sections of this material showed about half of the cells to be stained brown.

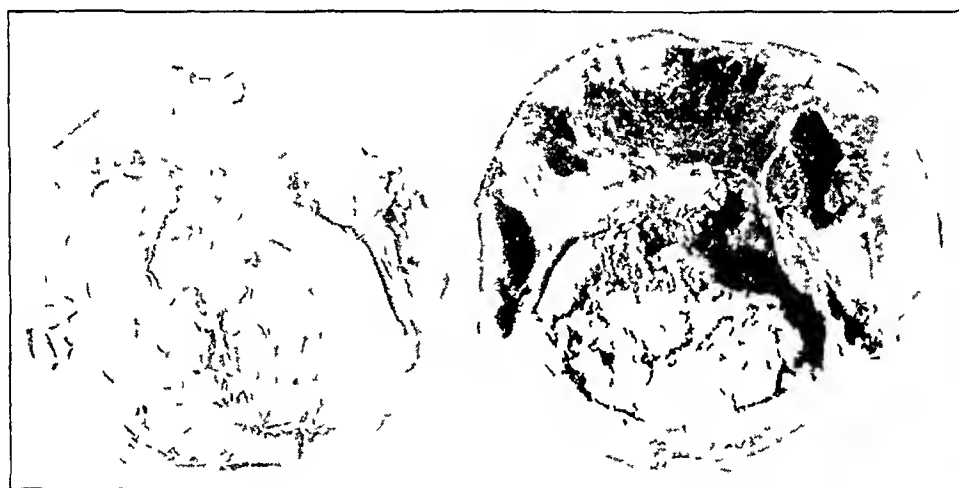
Sections stained by the Giemsa method showed green granules in the cytoplasm, such as are said to be specific for chromaffin cells.

In general the microscopic picture agreed with that of other reported chromaffin cell tumors.

**Diagnosis** The diagnosis was pheochromocytoma of the medulla of the adrenal gland.

**Report of Biochemical Examination**—Two samples of tumor tissue on analysis were found to contain, respectively, 345 and 353 mg per hundred grams of wet tissue of reducing substance (calculated as epinephrine).

Vulpian, Comessatti and diazo tests for epinephrine were performed on the extracts prepared from the tissue and found to be positive. A drop of each extract placed on the conjunctiva of a rabbit's eye caused narrowing of the blood vessels and blanching of the area.



A

B

Fig 3—*A*, the gross specimen before sectioning. The remnant of the normal adrenal gland is distinctively shown. The light spots on the surface are also flattened remnants of the adrenal cortex. *B*, the sectioned gross specimen, showing cystic degeneration.

Two samples were also taken from a central necrotic portion of the tumor. Extracts of these gave negative reactions to tests for epinephrine, and the color in the quantitative determination was of the same order as that observed in the blank determination, so not more than a trace of epinephrine was present in this part of the tumor.

The quantitative method used was a modification of that described by Folin, Cannon and Denis,<sup>4</sup> using the reagent described by Benedict<sup>5</sup> for the determination of uric acid.

4 Folin, O., Cannon, W. D., and Denis, W. A New Colorimetric Method for the Determination of Epinephrine, *J Biol Chem* **13** 477, 1912-1913.

5 Benedict, S. R. Determination of Uric Acid in Blood, *J Biol Chem* **51** 187 (March) 1922, Determination of Uric Acid, *ibid* **54** 233 (Oct) 1922.

*Electrocardiographic Findings*—During the last few months of the patient's illness, several electrocardiograms were taken, which revealed unusual abnormalities in the cardiac mechanism. So far as we know, similar abnormalities have not been reported in this condition previously. Previous reports which have included electrocardiographic studies have

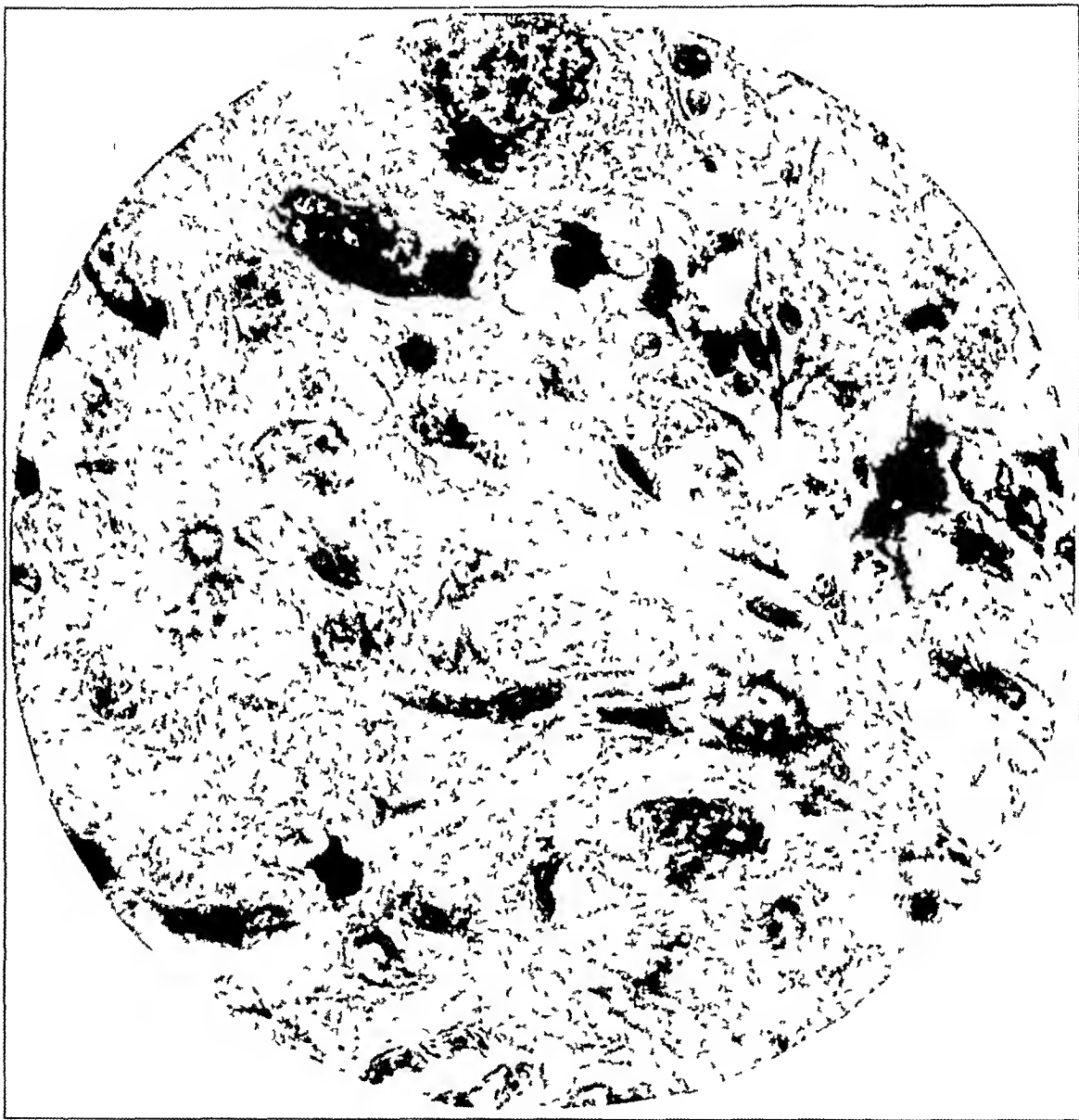


Fig. 4—High power photomicrograph of a section from the tumor. The abundant granular cytoplasm, the indistinct cell boundaries and the tendency to the formation of a syncytium are evident.

usually described a sino-auricular tachycardia, without other abnormality. In the case reported by Collier, Field and Durant<sup>2</sup> the T waves were inverted in leads I and II.

The findings in our case are perhaps best presented by direct reference to the tracings selected for reproduction. In them are included the significant abnormalities observed.

Tracing *A* in figure 5 (the three small strips above) was taken about forty-five minutes after an attack, at a time when the patient had no symptoms. There was still some residual tachycardia (pulse rate 103) from the previous attack, but the tracing is the most nearly normal for this patient that is available. The P waves are unusually high in lead II but less so than during some of the attacks. At such times some of the P waves in lead II were 5 mm. in amplitude.

The longer tracing (*B*) was taken during an attack and revealed coupled beats of rather unusual origin. Every other beat appeared to originate in the auriculo-ventricular node. These auriculoventricular nodal beats were slightly higher than those of sino-auricular origin and showed a slight notching on the upstroke of the R wave. This abnormality in rhythm apparently arose because the auriculo-ventricular node for some unknown reason had become more irritable than the sino-auricular node, which in turn appeared to be somewhat depressed. The auricles were beating slowly and regularly at a rate of 55, the interval between auricular beats being 11 seconds. The auriculoventricular node escaped at a

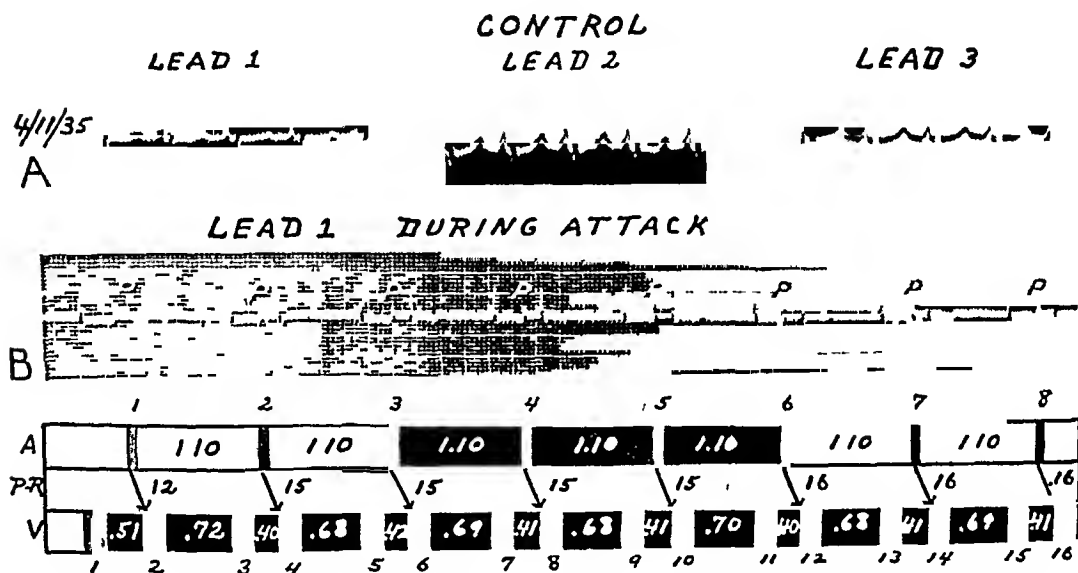


Fig 5—The diagrams beneath the longer tracing in figure 5 and the continuous tracing in figure 6 are arranged in identical fashion and may be described together. The black bars in the top strip of the diagram marked "A" represent the auricular waves and are placed directly beneath the P waves in the accompanying electrocardiogram. The interval between auricular beats is recorded in hundredths of a second. In the middle strip (marked "P-R") are recorded the PR intervals in hundredths of a second. When conduction of a beat between the auricle and the ventricle is thought to occur it is represented by an arrow. In the bottom strip, marked "V," the heavy black bars represent and are placed directly beneath the ventricular beats. Again the interval between the beats is recorded in hundredths of a second. Tracing *A* was made on April 11, 1935, and tracing *B* on March 30, 1935.

fairly constant interval after the beat of sino-auricular origin (0.68 to 0.72 seconds in *B*). Thus, the auriculoventricular node was considerably more irritable than the sino-auricular node.

Apparently the condition known as unidirectional block was present—that is, beats originating in the auriculoventricular node were not conducted back to the auricles, while beats originating in the sino-auricular node were readily conducted

to the ventricles. Thus the slower sino-auricular node was protected from the faster auriculoventricular node, otherwise the usual type of auriculoventricular nodal rhythm would have resulted.

One of us has on file data concerning several cases in which this disturbance of rhythm occurred, and as a subsequent report on this subject is planned, further discussion of the mechanism involved in this tracing will be deferred.

The abnormality in rhythm shown in figure 6 is similar to that present in figure 5*B*. The blood pressure was recorded simultaneously with the taking of this tracing and was observed to be 240 systolic and 170 diastolic. Again the auricular

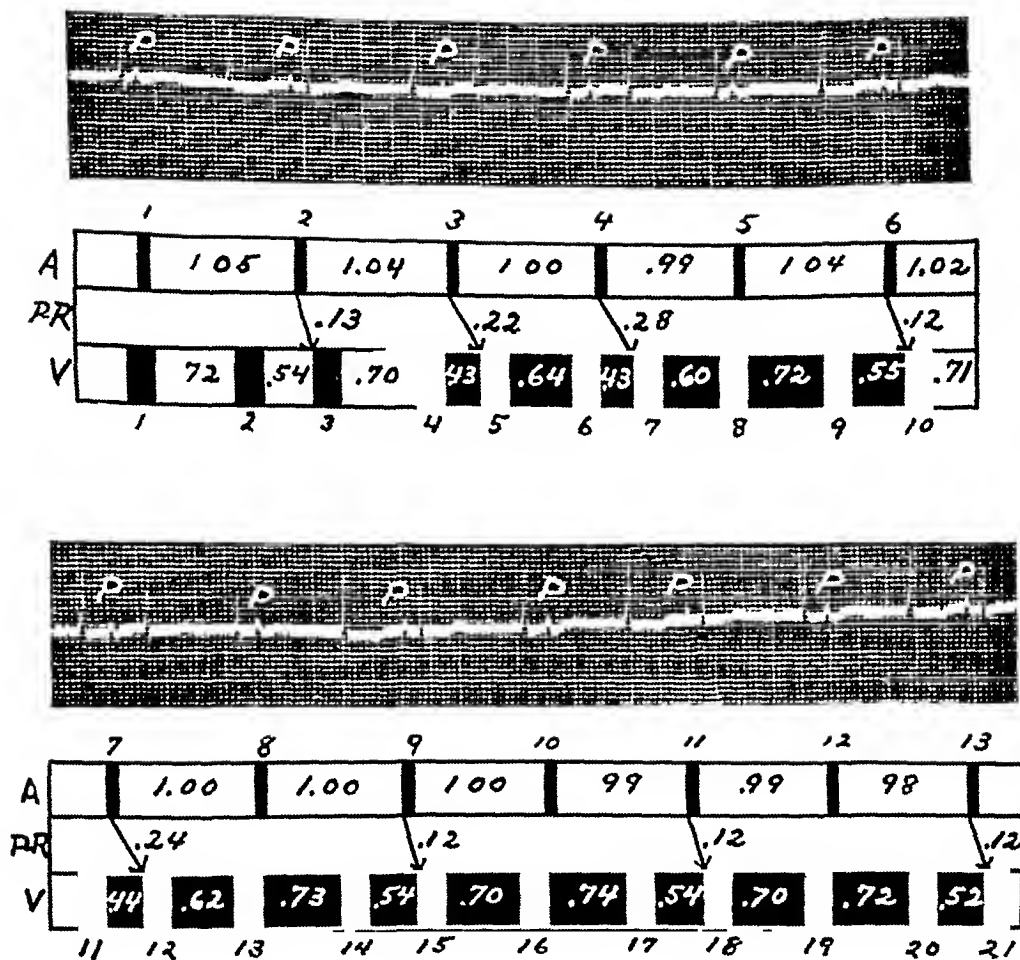


Fig 6—A continuous tracing in lead 1 taken on April 6, 1935. The explanation of the accompanying diagram is the same as that for the diagram in figure 5.

rate was slow but not so regular as that shown in figure 5, the interval between P waves varying from 0.98 to 1.05 seconds. As before, the nodal beats were usually higher and more notched than the normal beats, but this was not invariably so, as the nodal beats at times closely resembled those of sino-auricular origin (ventricular beats 1, 6, 8 and 13). The reason for this is not clear.

When the P wave fell shortly after the QRS complex, the ventricles either did not respond at all (auricular beats 1 and 5), or if the RP interval was somewhat longer, responded only after a prolonged PR interval (auricular beats 3, 4 and 7). In the former instance the ventricles were entirely refractory and in the latter partially so. As in tracing *B* in figure 5, the auriculoventricular node



escaped after about 0.7 second—that is, the rhythm during an attack was about 85 beats per minute. The interval between ventricular beats was shorter (for example, the intervals between ventricular beats 7 and 8) after a beat with a long PR interval (ventricular beat 7). This was apparently related to the long PR interval and suggests that the auriculoventricular node had already started to build up a new impulse before the previous excitation wave of sino-auricular origin had completely traversed the lower portions of the partially refractory conducting system.

Figure 7 shows another type of abnormality recorded during an attack of moderate severity. The chief variation from normal was in the P waves. They varied in shape, amplitude and direction. The amplitude of the P waves varied from +4 mm to -2 mm. As would be expected, the rate was generally faster with the high P waves and slower with the inverted P waves. The high P waves probably originated in the upper portions of the sino-auricular node, while the

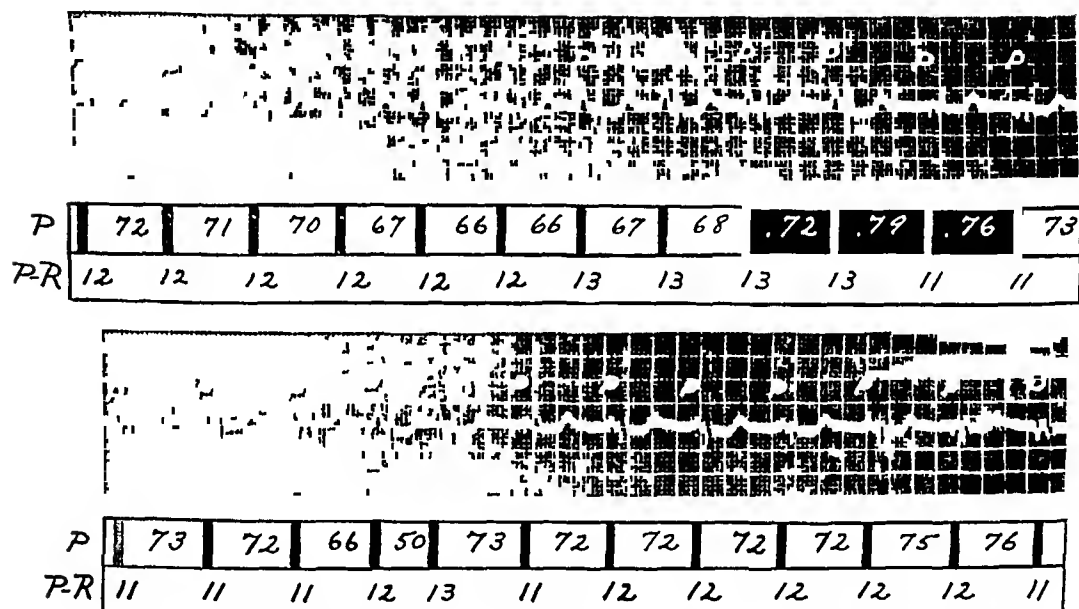


Fig 7—A continuous tracing in lead 2 taken on April 16, 1935. In the accompanying diagram the bars in the top strip, marked "P," represent and are placed directly beneath the auricular waves. The interval between beats is again recorded in hundredths of a second. In the strip below, marked "P-R," the PR interval of each auricular beat is recorded beneath that beat in hundredths of a second.

inverted P waves probably arose in the upper portion of the auriculoventricular node. The PR interval was slightly shorter with the inverted P waves than with the tall upright P waves. This supports the suggestion as to point of origin of the waves, as the beats originating in the sino-auricular node have farther to travel before reaching the ventricle. No definite change in the QRS complex was observed.

*Comment*—The disturbances of rhythm illustrated in these tracings seemed to result primarily from varying degrees of stimulation of the auriculoventricular node, usually accompanied by varying degrees of depression of the sino-auricular node during attacks. The actual mechanism of this alteration is a matter for speculation. The evidence

at hand suggests that, in this patient at least, the generalized intense stimulation of the sympathetic nervous system that apparently occurs in these attacks stimulates the auriculoventricular node much more than the sino-auricular node.

It is rather probable that in this patient the auriculoventricular node was unusually susceptible to the stimulation occurring in the attacks. If irregularities of the pulse and of the electrocardiographic tracings were a usual part of the syndrome, they would probably have been observed in previously reported cases.

*Fluoroscopic Examination*—The pulmonary fields and the diaphragm appeared normal. The left ventricle appeared slightly enlarged in the anteroposterior and left oblique views. The other chambers of the heart and the aorta appeared normal.

During observation the patient had a typical attack of moderate severity. At first, during the period of nausea, the cardiac pulsations were notably diminished in amplitude. At that time the radial pulsation was also very weak. In from one to two minutes the cardiac pulsations became much stronger, and definite irregularities were noted, having the appearance of extrasystoles. This irregularity was also evident on palpating the radial pulse. In another one or two minutes the irregularity disappeared and the heart beat was regular, with good pulsations. The patient was then feeling much better. No definite change in the size of the heart during the attack was detected.

*Summary of Electrocardiographic and Fluoroscopic Findings*—Several electrocardiograms are presented and described, illustrating abnormalities that appeared during the attacks characterizing this patient's illness. The site of the formation of the impulse of the heart beat was seen to vary between the sino-auricular and the auriculoventricular node and apparently arose at various locations in these nodes. This appeared to result in this patient from periodic intense stimulation of the auriculoventricular node, at times accompanied by depression of the sino-auricular node. On fluoroscopic examination the outstanding finding was the small amplitude of the cardiac contractions during the early part of an attack, as contrasted with the full, easily visible contractions before and after the attack.

#### COMMENT

The foregoing case report serves to emphasize certain aspects of the subject. The striking nature of the attacks, especially the sudden transition from hypotension to hypertension, is certainly so different from anything else seen in ordinary clinical experience as to suggest the diagnosis at once to one familiar with the condition. The marked tendency to shock is well illustrated and indicates that surgical intervention, which offers the only hope of recovery, is fraught with the gravest danger. Our experience in this case suggests to us that the abdominal approach must ordinarily be the method of choice, as manipulation of the tumor before its blood vessels are clamped off is likely to be considerable when

a posterior incision is used, and such manipulation must be considered dangerous, as it seems probable that a flooding of the circulatory system with epinephrine may result. In this connection, it is of interest that Pincoffs has called attention to the fact that it is just after the tumor has been separated from the general circulation that profound symptoms of shock are likely to occur and, further, that in one of his patients pressure on the tumor during abdominal examination was always followed by an attack. We feel that if our patient could have been seen in an attack early in the course of the disease and if the condition could have been recognized and operation performed, recovery could have been expected. The brilliant results in some of the reported cases (C. H. Mayo,<sup>6</sup> Coller and his associates<sup>2</sup> and a few others) are encouraging. One is drawn to the conclusion that a favorable outcome depends on adequate surgical treatment after early diagnosis.

As regards the production of the clinical syndrome, it is evident that the symptoms cannot be explained except as a result of activity of the sympathetic nervous system. When one considers that the action of epinephrine is a stimulation of this system resulting in activities typical of sympathetic action and that experimentally the hypertension, vasoconstriction, vomiting, pulmonary edema, shock and death have been shown to result from its injection, one is led to the simple hypothesis that in the case of a pheochromocytoma the blood stream is flooded from time to time with large doses of epinephrine. This idea is supported by the observation in the case reported by Porter and Porter<sup>7</sup> that an attack was always brought on when the patient assumed certain definite positions and that in Pincoffs' patient, as mentioned, when pressure was made on the tumor through the abdominal wall, an attack resulted. In our own patient the occurrence of paroxysms at fifteen minute intervals throughout the greater part of a day while the patient lay quietly in bed is not easy of explanation, nor is the fact that during labor, which was normal, no attack was induced.

#### SUMMARY

A case is reported of pheochromocytoma of the right adrenal gland with a typical clinical picture, the adrenal sympathetic syndrome and death after operative removal of the tumor.

No improvement was observed after roentgen treatment.

A study of the heart during the paroxysms showed with the onset of the hypertension a slowing of rate with a noticeable increase in

6 Mayo, C. H. Paroxysmal Hypertension with Tumor of the Retroperitoneal Nerve. Report of Case, *J. A. M. A.* 89:1047 (Sept. 24) 1927.

7 Porter, M. F., and Porter, M. F., Jr. Report of Case of Paroxysmal Hypertension Cured by Removal of Adrenal Tumor, *Surg., Gynec. & Obst.* 50:160 (Jan.) 1930.

the loudness of the sounds and an irregularity of rhythm associated with migration of the pacemaker. It seems probable that many of these changes constitute the cardiovascular reaction to sympathetic stimulation caused by the discharge of large amounts of epinephrine from the tumor into the circulating blood.

In view of the striking clinical picture which these patients present, it is to be hoped that in the future the diagnosis may be suspected early, the condition investigated thoroughly and early operation undertaken. In the more obscure cases we believe that a suspicious clinical picture, with characteristic changes of blood pressure will justify exploratory operation if the diagnosis cannot be made otherwise, in view of the importance of early diagnosis and the possibility of cure by surgical means.

# THE ADRENAL GLANDS

## A CLINICAL AND PATHOLOGIC STUDY

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LOS ANGELES

The relative infrequency of lesions of the adrenal glands becomes apparent when one examines statistical surveys of necropsies. In all probability this accounts for the slight attention given such lesions in the past. Increasing interest in the endocrine glands during recent years, however, has greatly stimulated the study of pathologic changes in the adrenal glands. It is often difficult to establish the presence of lesions of the adrenal glands in the living patient, the symptoms and signs may be indefinite compared to the extent of the lesion observed at autopsy. Again, symptoms referable to the adrenal glands may be obscured by those of a more acute and fulminating disease. During the past six years, in the course of performing routine necropsies, we have collected 39 instances demonstrating pathologic changes in these organs. In view of the fact that knowledge of these glands still remains incomplete, the clinical and pathologic observations made in the 39 instances have been studied. The purpose of this study was to correlate the clinical symptoms with the observations at autopsy, in the hope that the clinician and pathologist in the future might be more alive to the possibility of lesions in the adrenal glands.

The lesions of the adrenal glands in this series may be divided into three groups, as shown in the table. The basis for the division is pathophysiologic. In the first group, symptoms of acute adrenal insufficiency are present. These are often the result of hemorrhages into the adrenal glands. This condition is frequent in the new-born, in whom hemorrhages into both adrenal glands are prone to occur. In older children and in adults acute disturbances of the adrenal glands are not common. The medical literature contains only about one-hundred records of such cases<sup>1</sup>. In this condition the acute symptoms are often attendant on thrombosis of the adrenal veins, with hemorrhagic infarction of the glands. It would appear from a brief survey of the table that hem-

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1 Seligman, Bernard. Suprarenal Hemorrhage in the Adult, with Especial Reference to Hyperpyrexia, M J & Rec **135** 209, 1932

orrhage into the adrenal glands of adults is far from rare. It is interesting to note that greater numbers of such hemorrhages are recorded in the recent medical literature. This does not imply an absolute increase in the incidence but is the result of more accurate and detailed observations on the adrenal glands.

The second group which includes the growths in the majority of cases, takes into consideration those adrenal lesions which are of a more chronic nature. The average duration is one year and may be as long as three years. Addison's disease is the classic example. The Addisonian syndrome is usually due to tuberculosis of the adrenal glands, although other causes, such as atrophy, may operate to give a similar clinical picture. When the records of large series of autopsies were examined it was found that the incidence of Addison's disease was less than 1 per cent. In Ophuls' <sup>2</sup> series of 3,000 autopsies there were 13 instances

*Pathophysiologic Classification of Lesions of the Adrenal Glands*

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A	Acute adrenal insufficiency	
	I Hemorrhage	
	(a) In the new-born	4
	(b) In older children	1
	(c) In adults	5
B	Chronic adrenal insufficiency	
	(a) Atrophy	5
	(b) Simmonds' disease	1
	(c) Addison's disease	5
	(d) Coccioidial granuloma	1
	(e) Secondary neoplasm	3
C	Chronic adrenal hyperfunction	
	I Hypertrophy	
	(a) Diffuse	1
	(b) Compensatory	1
	II Cortical neoplasm	
	(a) Adenoma	11
	(b) Carcinoma	1

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(0.43 per cent) of Addison's disease. In 1924 in the registration area of the United States 363 deaths (0.3 per cent) were ascribed to Addison's disease of a total of 1,173,990 <sup>3</sup>. A review <sup>4</sup> of 25,000 autopsies performed at the Philadelphia General Hospital from 1867 to 1932 showed 55 (0.22 per cent) cases in which tuberculosis of the adrenal glands was observed, with symptoms of Addison's disease in only 11 (0.04 per cent). A series of 12,000 necropsies from the Leeds General Infirmary <sup>5</sup> showed 24 cases that revealed tuberculosis of the adrenal

<sup>2</sup> Ophuls, William. A Statistical Survey of Three Thousand Autopsies, Stanford University, Calif., Stanford University Press, 1926, p. 297.

<sup>3</sup> Guttman, P. H. Addison's Disease. A Statistical Analysis of Five Hundred and Sixty-Six Cases and a Study of the Pathology, Arch. Path. **10** 742 (Nov.), 895 (Dec.) 1930.

<sup>4</sup> Clark, J. H., and Rowntree, L. G. Studies of the Adrenal Glands in Health and Disease, Endocrinology **18** 256, 1934.

<sup>5</sup> Hellier, F. F. The Incidence of Atrophy and Tuberculosis of the Adrenal Glands and Their Relation to Addison's Disease, J. Path. & Bact. **33** 761, 1930.

glands, but an Addisonian syndrome occurred in only 9 instances (0.075 per cent). At the University College Hospital, London, 5,195 autopsies showed a total of 23 (0.44 per cent) deaths from Addison's disease.<sup>6</sup>

The third group includes benign and malignant neoplasms. The patients occasionally exhibit signs and symptoms of chronic hyperfunction of the adrenal glands. Hypertrophy of one adrenal gland is sometimes observed when the opposite gland has been destroyed by hemorrhage or tuberculosis. Simple bilateral hypertrophy is rare. Cortical adenoma is of relatively frequent occurrence, as shown in the table, but in many instances it does not produce any detectable clinical evidence of its presence. Geschickter<sup>7</sup> collected 72 instances of tumor of the adrenal cortex, 66 growths were benign adenomas, and the remaining 6 were carcinomas. In our series there is 1 example of carcinoma of the adrenal cortex, but primary tumor of the adrenal medulla is not represented.

#### ACUTE ADRENAL INSUFFICIENCY

*In the New-Born*—Extensive destruction of both adrenal glands by hemorrhage is inevitably fatal. This may occur in the absence of other lesions in other parts of the body. The clinical course is usually short. The diagnosis is difficult, it has been made in only a few instances during life. The presence of acute adrenal dysfunction should be suspected in fever of unknown origin, especially when it is associated with an increased rate of respiration and normal pulmonary findings. A yellowish pallor, cyanosis of the lips and finger-tips and a palpable mass in each flank are confirmatory signs.

Severe and fatal hemorrhage of both adrenal glands was encountered in the bodies of two new-born infants. It is interesting that these patients were identical twin girls (baby M1 and baby M2). Their symptoms, for the short duration of their lives, and the observations at autopsy were practically identical. Both were born at full term and were fairly well developed. At the time of delivery the respirations were slow and shallow and the heart sounds weak. Marked cyanosis of the visible mucous membranes and of the finger-tips was observed several hours after birth. One infant lived six, and the other eighteen, hours. At necropsy the lesions were confined to the adrenal glands. These were about three times larger than normal and contained much clotted blood. Microscopic examination of one adrenal gland showed widespread hemorrhage of recent origin in the medulla, with extension throughout the greater part of the cortex. The cortical cells were in various stages of degeneration, and only in a few small regions where there was little or no hemorrhage did they appear healthy. An interesting observation was the presence of small thrombi in some of the veins of the medulla.

<sup>6</sup> Barnard, W. G. Adrenal Atrophy in Addison's Disease, *J. Path. & Bact.* **33** 765, 1930.

<sup>7</sup> Geschickter, C. F. Suprarenal Tumors, *Am. J. Cancer* **23** 104, 1935.

The prognosis is more favorable when the adrenal hemorrhage is unilateral. It is therefore important that the clinician be able to recognize the signs and symptoms of adrenal insufficiency. Spontaneous recovery usually occurs if the hemorrhages are small. Massive unilateral hemorrhage often causes the same symptoms as bilateral hemorrhage. The presence of a mass in each flank makes the diagnosis of adrenal hematoma relatively certain. Intramuscular injections of whole blood may lead to recovery.<sup>8</sup> The administration of adrenal cortex hormone combined with blood transfusions may tide the infant over until organization of the hemorrhage has occurred or, perhaps, until the accessory cortical tissue has had an opportunity to undergo compensatory hypertrophy.<sup>9</sup> Intestinal obstruction in one instance was the result of pressure from a huge adrenal hematoma, excision of the mass led to recovery.<sup>10</sup> Hemorrhage of moderate severity in the adrenal glands may be associated with ecchymoses in other parts of the body. The adrenal hemorrhage may be only one manifestation of hemorrhagic diathesis in the newborn.

In an apparently normal boy (baby J) cyanosis and difficulty in respiration occurred several hours after birth. The administration of whole blood and dextrose caused some improvement. A second blood transfusion was given, with similar beneficial results. The cyanosis became extreme, and the infant died about one day after birth. At autopsy, the right adrenal gland was softened and hemorrhagic in the central portion, the left adrenal gland appeared normal. The adrenal lesion was complicated by moderate subdural and subtentorial hemorrhages. This combination of conditions was no doubt responsible for the fatal outcome. In another boy (baby C) respiration was established with difficulty. Death occurred shortly after birth. The left adrenal gland was soft and hemorrhagic, with necrosis of the medulla and the inner two thirds of the cortex. The right adrenal gland was grossly normal, but microscopic examination revealed congestion and a number of small hemorrhages in the cortex. A small subtentorial hemorrhage was the only other lesion in the body.

In the summation of these four records, two important common denominators are noted, viz., the difficulty in respiration and the cyanosis of the visible mucous membranes and the finger-tips. The temporary improvement brought about by blood transfusions in one baby is significant. It appears plausible that the administration of cortical hormone might have saved this infant's life, especially since the adrenal hemorrhage was unilateral and the cerebral injury slight.

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8 Rosenblum, Jacob. Suprarenal Hemorrhage in the New-Born Infant, *Am J Dis Child* **43** 663 (March) 1932.

9 Goldzieher, M. A., and Greenwald, H. M. Hemorrhage of the Suprarenals in the New-Born Infant. Diagnosis and Therapy, *Am J Dis Child* **36** 324 (Aug) 1928.

10 Corcoran, W. J., and Strauss, A. A. Suprarenal Hemorrhage in the New-Born, *J A M A* **82** 626 (Feb 23) 1924.



*In Older Children*—In older children punctate hemorrhages in the adrenal glands occur frequently during the course of infectious diseases. Larger hemorrhages are relatively uncommon and when they do occur are usually secondary to adrenal necrosis resulting from bacterial action or the effect of bacterial toxins.

A dramatic illustration of extensive bilateral adrenal hemorrhage was observed in a 5½ year old boy (W. D.). Vomiting occurred suddenly, and within a few hours the patient became stuporous and cyanotic. The respirations were rapid, and a few râles were audible over the base of the right lung. The neck was rigid, the cerebrospinal fluid eight hours after the onset of symptoms was normal. The child failed to rally, despite the administration of antimeningococcus serum and cardiac stimulants. He died twelve hours after the onset of the clinical symptoms. At the autopsy both adrenal glands were completely infiltrated with blood. Microscopically, necrosis was evident in the cortical tissue. There was bilateral hemorrhagic bronchopneumonia, and in the meninges were small collections of purulent material from which a few diplococci were recovered on direct smear but none on culture. The fatal outcome was attributed to the adrenal hemorrhage, which occurred in the beginning of fulminating cerebrospinal fever.

*In Adults*—In adults hemorrhage into the adrenal glands most often follows thrombosis of both adrenal veins.<sup>11</sup> This is more likely to occur in persons with chronic heart disease or long-standing tuberculosis or during the course of an acute infectious disease. At times bacterial emboli<sup>12</sup> may be demonstrated in the small adrenal arteries.

It is difficult and usually impossible to recognize the existence of an adrenal hematoma during life. Symptoms may be absent.<sup>13</sup> Hemorrhage, however, may be suspected in persons who complain of severe abdominal pain in the absence of physical signs, especially during the course of an acute infection. Asthenia, accompanied by a gradual fall in the blood pressure and a rise in the temperature, is observed at times. When bilateral hemorrhagic infarction of the adrenal glands occurs in the course of an overwhelming infection, the symptoms of the latter may completely mask any signs of acute adrenal disturbance. This happened in an otherwise normal and healthy white man.

In J. K., 33 years of age, the usual signs of lobar pneumonia were first detected in the lower lobe of the right lung, the process spreading within a few days to all the pulmonary fields. Death occurred nine days after the onset. The lungs, with the exception of the upper lobe of the left lung, were in a state of gray hepatization. Both adrenal glands were from three to four times larger than

11 Simmonds, M. Ueber Nebennierenblutungen, *Virchows Arch f. path. Anat.* **170** 242, 1902. Dudgeon, L. S. On Etiology, Pathology and Diagnosis of Adrenal Hemorrhage, *Am. J. M. Sc.* **127** 134, 1904. Pearl, F., and Brunn, H. Suprarenal Apoplexy, Bilateral, *Surg., Gynec. & Obst.* **47** 393, 1928.

12 Kovacs, Andreas. Beiderseitige akute Nebennierenblutung bei Influenza, *Frankfurt Ztschr. f. Path.* **38** 387, 1929.

13 Arnaud, F. Les hemorrhagies des capsules surrénales, *Arch. gén. de med.* **4** 5, 1900.

normal (fig 1) This increase was due to extensive recent hemorrhage Microscopic examination showed that the medulla was distended with blood, and the large veins contained hyaline thrombi from 1 to 3 mm in diameter The cortex contained recent extravasations of blood in all parts, and there was marked necrosis of much of the cortical tissue The fibrils of the adrenal capsules were spread apart by hemorrhage, and in many places bleeding had extended far beyond the capsular boundaries Sections stained by the Gram-Weigert method failed to reveal any organisms

Severe abdominal pain developed in a man (D F R), 40 years of age, who had apparently made a complete recovery after an attack of acute streptococcal tonsillitis This soon became worse and was most severe in the region of the left kidney The patient was extremely restless Rigidity developed on the left side of the abdomen Severe pain was then experienced on the right side, so that exploratory laparotomy was deemed advisable No abdominal lesions were observed The patient became progressively weaker, the pulse rate became more rapid, and the temperature rose to 104.6 F Death occurred two days after the

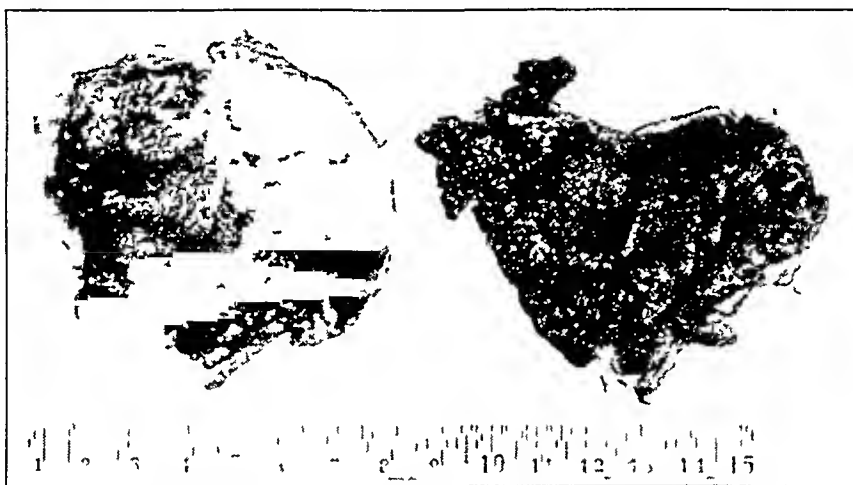


Fig 1 (J K) —Massive hemorrhage in both adrenal glands, secondary to lobar pneumonia

operation The only lesions to be seen at autopsy were in the adrenal glands Both adrenal glands were embedded in hematomas, and the glandular tissue was apparently necrotic (fig 2) Microscopically, both glands and much of the surrounding connective tissue were densely and diffusely infiltrated with blood Except for the presence of a few islands in the cortex, the epithelial cells were completely destroyed In a number of places the capsule appeared to be heavily infiltrated with neutrophils Many of the veins in the surrounding connective tissue, as well as those in the glands themselves, were filled with recent thrombi

Adrenal hemorrhage was also observed in an 18 year old girl (R T) This occurred in the early months of the patient's first pregnancy, which was complicated by severe hyperemesis gravidarum The sole lesion was in the adrenal glands There was extensive hemorrhage into the medulla and cortex of the left adrenal gland, while several smaller hemorrhages were observed in the gland on the right The microscopic picture resembled in many respects those described in the preceding records In this case also the medulla was distended by a recent

extravasation which was infiltrated in several places by large collections of polymorphonuclear leukocytes. Two large veins and a few smaller ones in the medulla were almost completely filled with thrombi.

Ecchymoses into the adrenal glands may be observed during the course of careful postmortem examinations in persons who have died of a variety of lesions. Such hemorrhages are not extensive. They do not give rise to symptoms, as a rule, but are included in this series because they demonstrate the relatively frequent occurrence of hemorrhage in the adrenal glands of adults.



Fig 2 (D F R) —Massive bilateral hemorrhage in the adrenal glands, secondary to tonsillitis (streptococcic)

In a man (V B), of 63 years, with aleukemic myelogenous leukemia microscopic examination revealed small hemorrhages in the medulla and the deeper parts of the cortex. Hyaline thrombi were seen in some of the arterioles and smaller veins. In another man (J Y), 76 years of age, in whom there was a carcinoma of the prostate, with extension and metastases, moderate hemorrhage had occurred into both adrenal glands. In many places the cortex was completely necrotic, while the medulla was well preserved.

#### CHRONIC ADRENAL INSUFFICIENCY

*Atrophy*—The term chronic adrenal insufficiency is nearly always associated in the physician's mind with a tuberculous process in the adrenal glands. This destructive lesion frequently results in the definite and well recognized clinical picture of Addison's disease. At post-mortem examination, however, in about one tenth of the persons who had signs of an addisonian syndrome during life the adrenal glands will be seen to be small, with no demonstrable evidence of tuberculosis.

The pathologic changes in many of these small atrophic glands are confined to the cortex, while in others extensive lesions are present in both the cortex and the medulla. Many names have been suggested for the condition, and one finds the lesions referred to as hypoplasia, simple or idiopathic atrophy, cirrhosis and cytotoxic contraction or primary contraction of the adrenal glands<sup>3</sup>. This variability in terminology reflects the present ignorance of the underlying pathologic process. Congenital hypoplasia of the adrenal glands has been suggested as a possible cause, but there are no facts to support this theory. Healed tuberculous processes with extensive scarring are also a theoretical possibility. There has been no proved instance of healed tuberculosis of the adrenal glands<sup>4</sup>. Syphilitic infections have been incriminated without an adequate pathologic basis for such a contention<sup>14</sup>.

There is a striking resemblance between atrophy of the adrenal glands and toxic necrosis of the liver, especially in the group of subchronic lesions. This suggests that a toxic agent may act selectively on the cells of the adrenal cortex<sup>15</sup> in much the same manner as certain poisons are believed to destroy the liver cells. The toxic agent which is thought to injure the adrenal cortex must be continuous or at least intermittent in its action over a considerable period. Lesions in the medulla are secondary to those in the cortex. In the end the regenerative capacity of the cortex may become inadequate, and clinical evidence of adrenal insufficiency becomes apparent. There is no evidence as to the nature of the agent which brings about slow degeneration of the cortical cells. One must conclude that the etiology is still unknown. Accurate pathologic studies of adrenal glands showing primary contraction are of value in determining the functions of the adrenal cortex and the medulla. Such studies should also give a better understanding of the underlying forces operative in the production of the Addisonian syndrome.

The medical literature contains a series of interesting records of primary contraction of the adrenal glands<sup>16</sup>. Of some import, perhaps,

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14 Simmonds, M. Ueber Nebennierenschumpfung bei Morbus Addisoni, *Virchows Arch f path Anat* **172** 480, 1903.

15 Kovacs, Walther. Zur Nebennierenpathologie, *Beitr z path Anat u z allg Path* **79** 213, 1928.

16 (a) Bittorf, A. Die pathologie der Nebennieren und der Morbus Addisoni, Jena, Gustav Fischer, 1908. (b) Conybeare, J. J., and Millis, G. C. Observations on Twenty-Nine Cases of Addison's Disease Treated in Guy's Hospital Between 1904 and 1923, *Guy's Hosp Rep* **74** 369, 1924. (c) Harbitz, F. Suprarenals in Addison's Disease, *Norsk mag f lægevidensk* **87** 371, 1926. (d) Brenner, O. Addison's Disease with Atrophy of the Cortex of the Suprarenals, *Quart J Med* **85** 121, 1928. (e) Barker, Nelson W. The Pathologic Anatomy in Twenty-Eight Cases of Addison's Disease, *Arch Path* **8** 432 (Sept) 1929. (f) Wells, H. Gideon. Addison's Disease with Selective Destruction of the Suprarenal Cortex ("Suprarenal Cortex Atrophy"), *ibid* **10** 499 (Oct) 1930.

is the series of 9 cases of Addison's disease studied by Wells<sup>10f</sup>, in 6 the condition was of the atrophic type, and in only 3, of the tuberculous type. In the former there was nothing either in the clinical history or in the pathologic studies to explain the widespread destruction of the adrenal glands. A possible relation between influenza and adrenal atrophy is suggested. Many records will have to be examined before conclusions of value can be reached regarding the etiologic significance of influenza or other infections in the production of primary contraction of the adrenal glands.

There are no constant clinical features in Addison's disease which differentiate a tuberculous process from atrophy. Minor differences may be noted at times, which may favor either one process or the other. At times the blood pressure, although reduced, is at a relatively higher level in persons suffering from adrenal atrophy. The higher pressure is attributed to a relative integrity of the medulla. Shortly before death the blood pressure usually sinks to a low level. Frequent blood pressure readings in cases of Addison's disease may be of value. Pigmentation of the skin has been the only clinical feature observed over a period of several years in some persons with primary contraction of the adrenal glands, occasionally a dark skin has been present since childhood. Unfortunately, chronic adrenal insufficiency is not always accompanied by darkening of the skin, and it is in this group that there is the greatest difficulty in diagnosis.

The relative infrequency of primary contraction of the adrenal glands and the unrevealed etiology are sufficient reasons for reporting the present series of five records. Pigmentation and clinical signs of adrenal insufficiency were present in 2.

In a woman (P. C. T.), 50 years of age, who had always had a dark skin, pigmentation had become more noticeable during the last two years of life. The increase in pigmentation followed an attack of influenza and was associated with progressive weakness, and the blood pressure was apparently low. Gastrointestinal disturbances were present a few days before death. It is interesting that this woman was seen by a physician for the first time only two days before her death. She appeared well developed and well nourished. Pigmentation was observed in the skin of the face, neck, forearms and inner surfaces of the elbows and thighs and on the labia. The general condition seemed fair, but she died suddenly and unexpectedly. At autopsy the right adrenal gland appeared to be absent. The left gland, which was very small, measured 2 by 1.5 by 0.3 cm. Sections from the region of both adrenal glands showed small remnants of the cortex and medulla surrounded by dense cicatricial tissue, heavily infiltrated by round cells. There was hypertrophy of the cortical cells, some having developed into giant cells (fig. 3). The small adrenal glands were associated with brown atrophy of the heart and atrophy of the ovaries and the breasts.

In another strongly built and well nourished woman (H.), 50 years of age, pigmentation of the skin, weakness, loss of weight and nervousness were present for one year. Rest in bed failed to improve the general condition. She became

progressively weaker and had attacks of syncope. Precordial pain and a friction rub over the cardiac area led to a diagnosis of acute pericarditis. The blood pressure was 110 systolic and 80 diastolic, the skin was scaly, and the tissues were flabby. Hypothyroidism and hypo-adrenia were suspected. Thyroid extract administered by mouth and epinephrine hydrochloride given intramuscularly improved the general condition, but the precordial pain and anginal attacks persisted, so that the patient was kept in bed. Terminal bronchopneumonia hastened her death. Autopsy showed a normal pericardium and moderate but generalized senile arteriosclerosis, with some cardiac hypertrophy. Each adrenal gland was embedded in adipose tissue and was from one-half to two-thirds the normal size.



Fig 3 (P C T) —Photomicrograph showing chronic adrenalitis with atrophy and fibrous thickening of the capsule. The zonal architecture of the cortex is completely obliterated.

Microscopically, the capsule was thickened, and there were a few lymphocytes between the fibrils. In the thinner portions of the gland there was no medulla and the cortex was decreased in width, although there was a suggestion of the usual layers. The pale cortical cells contained considerable lipid. Relatively large islands of medullary cells were present in the thicker portions of each gland. With connective tissue stains some increase in the fibrous stroma was apparent in both the cortex and the medulla.

The following clinical history of a 32 year old woman (M C) who died suddenly during the administration of an anesthetic is very instructive. All her

complaints dated from the birth of a child ten years previously. At this time a "physical and mental breakdown" occurred. Labor had been prolonged but was normal in all other respects. After an attack of influenza a year previously she regained her strength very slowly. At the time of her last admission to the hospital she complained of a tired feeling and a bearing-down sensation in the lower part of the abdomen. She appeared very nervous. There were a cystocele, a rectocele and a shallow cervical tear. The blood pressure was 98 systolic and 78 diastolic, and the pulse rate was 100. With rest in bed the systolic pressure rose to 115 mm of mercury, and the pulse rate varied between 74 and 80. The patient became less nervous and appeared to be in good condition for an operation. Thirty grains (0.2 Gm) of chlorbutanol was given preoperatively. The

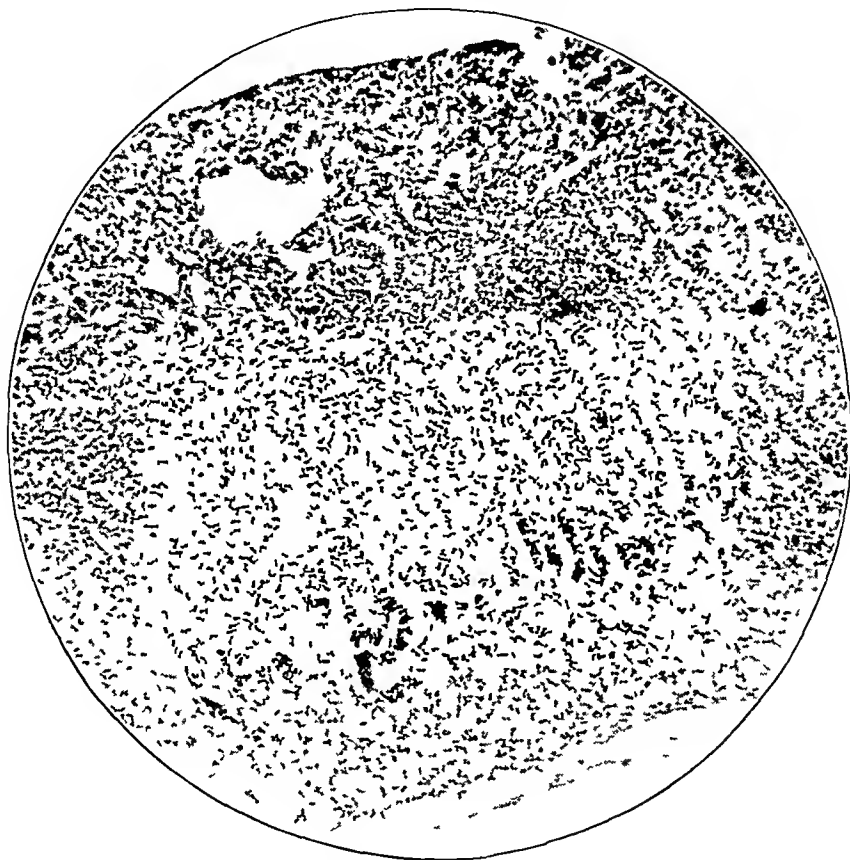


Fig 4 (M C) —Photomicrograph showing marked atrophy of the adrenal cortex. This is true atrophy, with diminution in size of the individual cells. The various layers are poorly defined.

pulse was of good volume. Nitrous oxide gas was not tolerated well, the skin became dusky, and the respirations slow. Ethylene was substituted, but after a few minutes the pulse stopped. Artificial respiration and stimulants were of no avail.

Autopsy showed cyanosis of the lips, ears and neck. The left adrenal gland measured 2.5 cm in length and 4 mm in the thickest portion. The right gland was slightly smaller and was only 2 mm in its thickest part. Microscopically, the capsule was thickened. The zonal arrangement of the cortex was disturbed, and all the cortical cells were small (fig 4). The medulla consisted of only one or two small groups of cells. The right adrenal gland contained a few

minute cortical adenomas. These changes in the adrenal glands were associated with fatty changes in the liver, lipomatosis of the wall of the right ventricle of the heart and slight chronic bronchitis with peribronchial scarring.

The past history suggested that this patient had always been below par. She had been delicate as a child and had had rickets. When she was 11 years of age an acutely inflamed appendix was removed. At the age of 15 a "nervous breakdown" occurred. It seems logical to conclude that in this patient a moderate degree of adrenal insufficiency had been present for a number of years.

A woman (J S), of 38 years, had complained of dysmenorrhea for the past five years. The pain had become progressively severe. She had noticed a mass in the lower part of the abdomen about one and one-half years before consulting

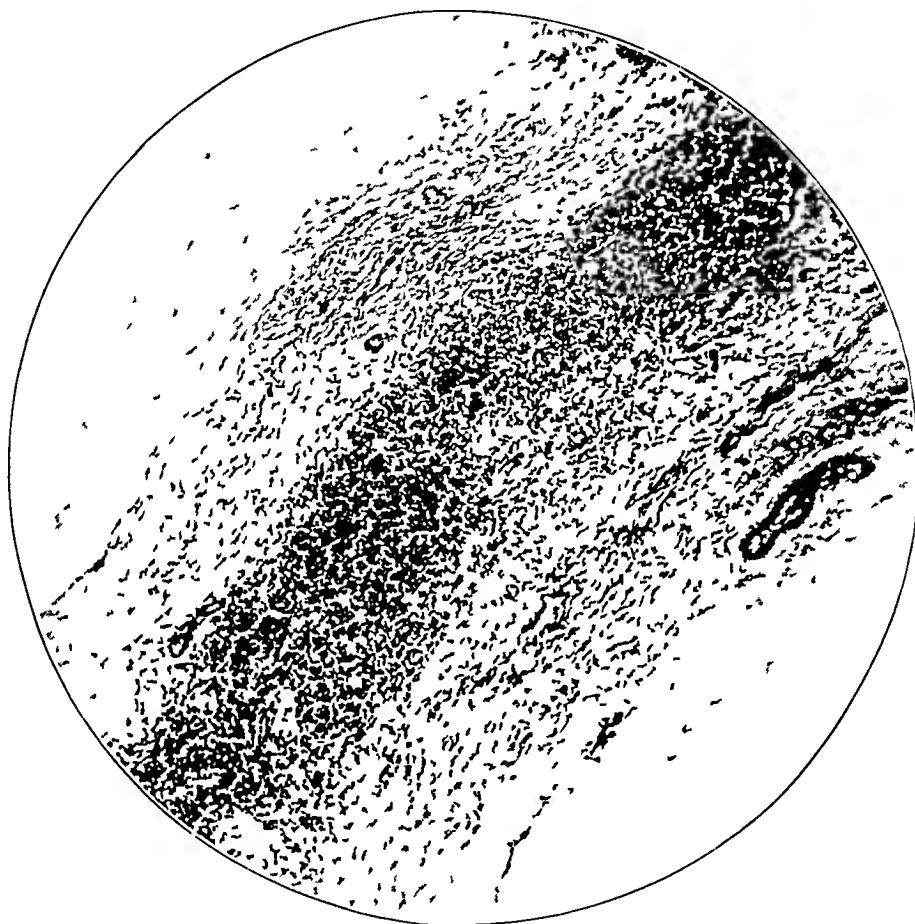


Fig 5 (J S) —Photomicrograph showing chronic inflammation of the adrenal gland, with marked capsular fibrosis and heavy diffuse infiltration by round cells

a physician. Examination revealed a firm nodular mass filling the pelvis. The blood pressure was 118 systolic and 72 diastolic. An operation was performed, and the uterus was removed. This was large, with several fibromyomas and bilateral ovarian cysts.

Soon after the operation the pulse became soft and very rapid and the hands cold and clammy. Fluids were given by hypodermoclysis, and the patient showed improvement. Late in the afternoon of the day of the operation sudden extreme shock with mild cerebral irritation occurred. Immediate improvement followed the intracardiac injection of 2 cc of a 1:1,000 dilution of epinephrine hydrochloride. Early in the evening the patient again went into shock. The intracardiac



injection of epinephrine hydrochloride resulted in some improvement, and from 15 to 20 minims of epinephrine hydrochloride was then given intravenously every forty-five minutes. With each injection transitory improvement was observed. The skin became an icteric color, and twitching of muscles and delirium occurred. The patient died about fifteen hours after the operation. At the necropsy the only evident lesions were in the adrenal glands, the right one being extremely small, with a thin cortex and softening of the central portion. The left gland was about one-third the normal size and only 2 mm in thickness. In the microscopic study the capsules of the glands were densely fibrous, with heavy collections of lymphocytes replacing the glandular tissue (fig 5). The cortex was almost completely destroyed except for a few small islands of regenerated cortical cells. There was no medulla.

A woman (M. L.), of 43 years, had recurrent attacks of epigastric pain for the last ten to fifteen years. During the last year there was much nausea, which was sometimes associated with vomiting. There was some radiation of pain to

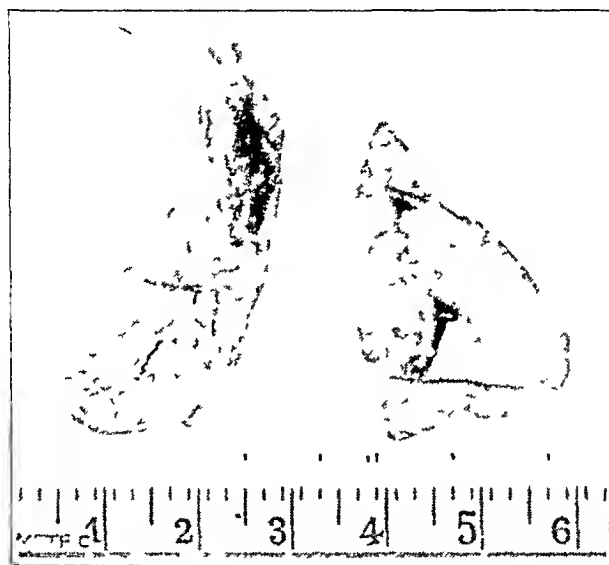


Fig 6 (M. L.)—Atrophy of the adrenal glands

the back. The patient was small, weighing only 100 pounds (45.4 Kg). The blood pressure was 95 systolic and 60 diastolic. Roentgen examination suggested pyloric obstruction from a healed ulcer. Surgical intervention for the alleviation of symptoms was deemed advisable. Numerous gallstones were removed from the gallbladder, and a gastro-enterostomy was done. She died suddenly and unexpectedly one month after the operation. At the postmortem examination signs of terminal bronchopneumonia with acute serofibrinous pleuritis were present. A small abscess was observed in the region of the surgical incision. There was chronic cholecystitis. The pylorus and duodenum were drawn up and fixed to the gallbladder by dense adhesions. The pyloric opening was small. There had been good healing of the gastro-enterostomy wound. The left adrenal gland weighed 26 Gm, and the right, 18 Gm (fig 6). Sections through the adrenal glands showed thickened capsules. The cortex was extremely narrow, and the cells had a disorderly arrangement. Small islands of medullary tissue were seen.

*Simmonds' Disease*—Polyglandular disease, or Simmonds' disease, is usually associated with small adrenal glands. There may be some

difficulty in differentiating between Simmonds' disease and the Addisonian syndrome clinically, particularly when pigmentation of the skin, hypotension and marked asthenia are present

Polyglandular disease was observed in a woman (R R) of 40 years. Her chief complaints were weakness and inability to withstand cold. She had the appearance of an emaciated woman of about 70 years. Her skin was yellow and dry, and there was a brown patchy pigmentation of her face. The scalp hair was very fine, axillary and pubic hair was absent. There was marked hypotension, the blood pressure was 80 systolic and 60 diastolic. A clinical diagnosis of Simmonds' disease was made, although Addison's disease was considered. The patient's weakness increased progressively until death.

At the postmortem examination all that could be seen of the pituitary gland was a small gelatinous residue of the posterior lobe. There was marked atrophy of most of the organs. The thyroid gland was small and weighed only 10 Gm, while the liver weighed 620 Gm and the weight of the combined kidneys was 160 Gm. There was marked atrophy of the ovaries, uterus, vagina and mammary glands. The adrenal glands were about one-third the normal size. Microscopically, both had capsules of dense connective tissue. The cortex was absent in some places, and in others three layers were present. Many of the cortical cells were necrotic. The medullary cells were indefinitely outlined and most of the nuclei appeared pyknotic. In the left gland the medulla was almost completely absent and was replaced by connective tissue markedly infiltrated with round cells.

*Addison's Disease*—Addison's disease usually results from tuberculosis of both adrenal glands and produces a well recognized clinical picture. The salient features are illustrated in the following brief clinical and pathologic records.

The chief complaints of a woman (D B), of 33 years, were general weakness, loss of weight and gastric disturbances. These symptoms had become more pronounced following an attack of influenza seven months before death. Darkening of the skin was first noticed after this infection. She was fairly well developed and showed splotchy pigmentation of the neck, back, abdomen and extremities. The buccal mucosa was also pigmented. There was atrophy of the muscles of the extremities. Blood pressure readings were consistently low, the systolic pressure was 88 mm of mercury ten days before death and gradually dropped to 76 mm. A clinical diagnosis of Addison's disease was made.

At the autopsy both adrenal glands were large, confluent regions of caseous necrosis were seen grossly, but normal adrenal tissue was not in evidence. Microscopically, caseous areas were bounded by fibrous tissue containing many round cells and a few cellular tubercles. No adrenal tissue was observed. Smears contained many acid-fast bacilli. There were small partially healed tuberculous foci in the lungs and peribronchial lymph nodes and evidence of active tuberculosis in the ileum.

In a woman (F D), of 40 years, the major complaints were weakness and loss of weight. The onset occurred a year previously, with pain in the joints and severe infection of the teeth and gums. At the time of her last admission to the hospital she was greatly emaciated. There was brown pigmentation of the skin of the hands and elbows. The teeth were loosened by the existing purulent gingivitis. She became irrational, requiring restraint, and died shortly after admission. Large adrenal glands weighing 40 Gm were observed at the autopsy. The

normal architecture was replaced by homogeneous grayish firm tissue. A few regions of caseation were visible in the left gland. Microscopically, there was much tuberculous granulation tissue containing many solitary and confluent tubercles abounding in giant cells. A few areas of caseation were noted, and these were surrounded by dense fibrous tissue. A Ghon tubercle was noted in the apex of the left lung. The heart and aorta were hypoplastic, the thymus measured 7 by 6.5 by 1 cm.

The third observation was made on a man (H. H.), 58 years of age, who had complained of progressive weakness for the past nine months. During the last few weeks he had been recumbent most of the time. There was a feeling of coldness of the extremities and extreme nausea at the sight of food. The skin over most of the body was burned brown by the sun, but shortly before death this pigmentation increased. The systolic pressure was very low (80 mm of mercury). There was weakness of the extremities, and muscle tone was deficient. Although the patient rallied somewhat after a blood transfusion and a subcutaneous injection of extract of adrenal cortex, he continued to become weaker, lapsing into a state of drowsiness just before death.

Both adrenal glands were of normal size but had irregular contours and contained firm caseous regions which had apparently replaced all the normal glandular tissue. Histologically, large caseous areas were surrounded by tuberculous granulation and fibrous tissue (fig. 7). Narrow bands of cortical cells were seen in the right adrenal gland but were not present in the left. Focal, partially healed tuberculous lesions were observed in the apex of both lungs and in the peribronchial lymph nodes.

Extensive destruction of the adrenal glands by tuberculosis does not always give rise to definite symptoms. Patients with this condition may die suddenly in the same manner as those with primary contraction of the adrenal glands. This is shown in the following observation.

A man (T. M.), 39 years of age, consulted a physician because he had noticed blood in the urine. At times he had had protracted chills after urination, and these had always left him weak and exhausted. Physical examination revealed dark pigmented areas on the face, hands, back and abdomen. The gums and buccal mucosae were also pigmented. The blood pressure was 115 systolic and 50 diastolic. Pyelograms failed to outline the calices of the lower pole of the right kidney. The left kidney produced a normal shadow. Nephrectomy was performed. The right kidney had a large solitary cyst in its lower pole. The patient died suddenly the morning after the operation. At the postmortem examination the adrenal glands were seen to be normal in size but showed irregular areas of caseation. Histologically, these were surrounded by fibrous tissue and contained some atypical tubercles. A small remnant of adrenal tissue was seen in only one place. There were signs of terminal acute hemorrhagic bronchopneumonia, and small, apparently quiescent, tuberculous foci were present in the apexes of both lungs.

It may occasionally be difficult, even impossible, to determine the etiologic agent which has destroyed a great part of the suprarenal tissue.

In a man (A. H.), of 64 years, the usual signs and symptoms of prostatic hypertrophy were present. A first blood pressure reading revealed moderate hypotension, the pressure being 120 systolic and 78 diastolic, two subsequent readings were 100 systolic and 65 diastolic and 105 systolic and 70 diastolic, respectively. The histamine skin test for adrenal function was unsatisfactory. A first stage operation for an enlarged prostate gland was withstood well, and the systolic

pressure on the subsequent days remained between 120 and 124 mm of mercury. The second stage operation was performed nine days after the first one. Soon after the operation the patient passed into profound shock, the pulse rate became rapid (from 140 to 150), and death occurred two days later. At the autopsy a brownish mottling of the skin of the abdomen and about the external genitalia was noted. The interesting lesions were in the adrenal glands. The left gland was represented by a calcified scar and one or two small bits of adrenal cortex. The right gland was about normal in size and measured 4.5 by 3 by 0.3 cm. It contained one small region of calcification and a small adenoma. Microscopically, the left adrenal gland had a thickened fibrous capsule; there was only a small amount of degenerated cortical tissue remaining, which was surrounded by fibrous tissue and heavy calcific deposits. In the right gland a goodly amount of cortical tissue was present, the cortical cells contained many tiny globules of fat, which were much smaller and more diffuse than the normal globules of lipid. Dense

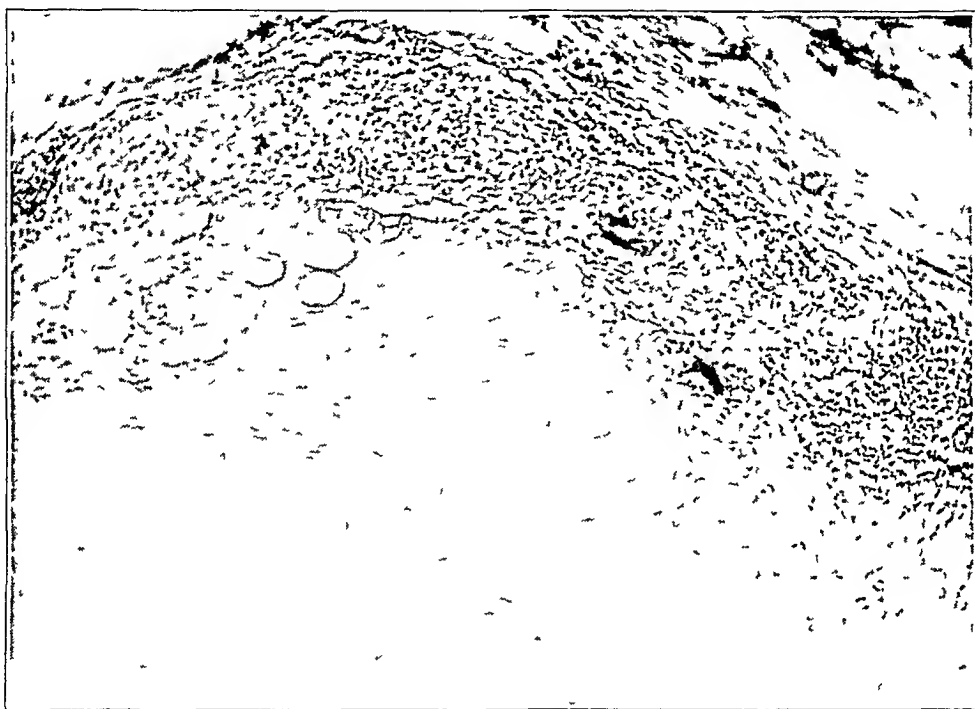


Fig 7 (H. H.)—Photomicrograph showing a typical area of a tuberculous adrenal gland. A large area of caseation is bordered by tuberculous granulation tissue in which small tubercles and several Langhans giant cells are seen.

fibrous tissue containing many round cells had grown between the cortical cells, and there were two small regions of calcareous degeneration. The medulla was reduced in amount, and in its place were many round cells. A small, partially healed tuberculous focus in the apex of the left lung was the only evidence of past infection.

*Coccidioidal Granuloma*—The record of a woman (I. H.), 45 years of age, deserves mention. Symptoms suggesting pulmonary tuberculosis had been present for about three months. These were complicated by meningitis in the last two weeks of life. *Coccidioides immitis* was demonstrated in cultures of the spinal fluid and in those of material from an enlarged posterior auricular lymph node one week before death. At the necropsy lesions produced by these organisms were observed in the nose, meninges, lungs and cervical and retroperitoneal lymph nodes.

and in the spleen, kidneys and adrenal glands. The latter were considerably enlarged, and microscopically there was abundant granulation tissue, with areas of caseation and giant cells containing the doubly contoured spores. The medulla was destroyed, and there was considerable encroachment on the cortex of each gland. Death resulted primarily from the meningeal involvement. The destruction of the adrenal glands was not of sufficient duration to produce symptoms.

*Secondary Neoplasms*—A malignant tumor may metastasize to the adrenal glands, but there is usually no evidence of insufficiency. In the histologic examination of such glands numerous nests of functioning adrenal parenchyma are almost constantly present. The following cases are illustrative.

A woman (V J), of 55 years, had carcinoma of the breast. Metastases were widespread. Marked weakness during the last year of life kept her confined to bed. The asthenia seemed to be more extreme and more chronic than is ordinarily observed in carcinomatosis and is possibly attributable to destruction of the adrenal glands by the metastatic growths.

A carcinoma of the sigmoid flexure in a man (W W), of 62, had metastasized to the mesenteric lymph nodes and both adrenal glands. The symptoms, however, indicated a lesion in the lower part of the intestinal tract. The adrenal glands were large, soft and lobulated, normal adrenal tissue could not be recognized grossly. Histologically, masses of tumor cells were present throughout both glands, which were similar in their morphologic characteristics to the cells in the primary growth. Clusters of cortical cells were preserved in some places.

In a male student (E R), of 30 years, very large metastases from a melanoma of the back were observed in the adrenal glands. A pigmented nevus had been excised with difficulty about three years previously and had recurred twice within a year and a half. Numerous secondary growths developed in the skin of the chest and arms and in the axillary lymph nodes. The pronounced weakness, anorexia and emaciation that were present for several months before death may have been due in part to destruction of the adrenal glands. Contrary to the usual picture, the liver contained only a few tiny metastases. Each adrenal gland was replaced by a tumor almost as large as the corresponding kidney. Only small groups of atrophic cortical cells remained, the greater part of the glands being replaced by malignant growth.

#### CHRONIC ADRENAL HYPERFUNCTION

*Hypertrophy*—Simple diffuse hypertrophy of both adrenal glands is infrequent.

Bilateral hypertrophy of moderate degree was observed in a 38 year old woman (L G H) who died of a very malignant adenocarcinoma of the cecum. Hypertrichosis of the face, thighs and legs was the only indication of possible hyperfunction of the adrenal glands. The combined weight of the adrenal glands was 21 Gm, the measurements were 6.8 by 2 by 1.5 cm and 5.8 by 4 by 1.2 cm, respectively (fig 8). Microscopically, the cortex was considerably widened, the greater part consisting of the zona fasciculata. The medulla appeared normal.

Compensatory hypertrophy is more frequently observed. It was first described by Marchand (cited by Goldzieher) and follows the

unilateral destruction or the removal of one adrenal gland. This may be the result of a caseous process or may be due to unilateral aplasia. Experimental compensatory hypertrophy has been produced in albino rats<sup>17</sup>. Removal of one gland is followed by hypertrophy of the remaining one and is practically limited to the cortex.

In a man (H. G.), of 44 years, who died of bilateral bronchopneumonia the autopsy further disclosed hemachromatosis with involvement of the pancreas. Quiescent tuberculous foci were seen in the tracheobronchial lymph nodes. The right adrenal gland was small and consisted almost entirely of a dense yellow homogeneous mass with just visible tiny bits of cortex and medulla. Large, confluent regions of caseation were present microscopically, surrounded by small tubercles and tuberculous granulation tissue. Nests of cortical cells were occasionally seen. The left adrenal gland was about twice the usual size but appeared normal in every other respect. Microscopically, hypertrophy was marked in the cortex and present to a lesser degree in the medulla.

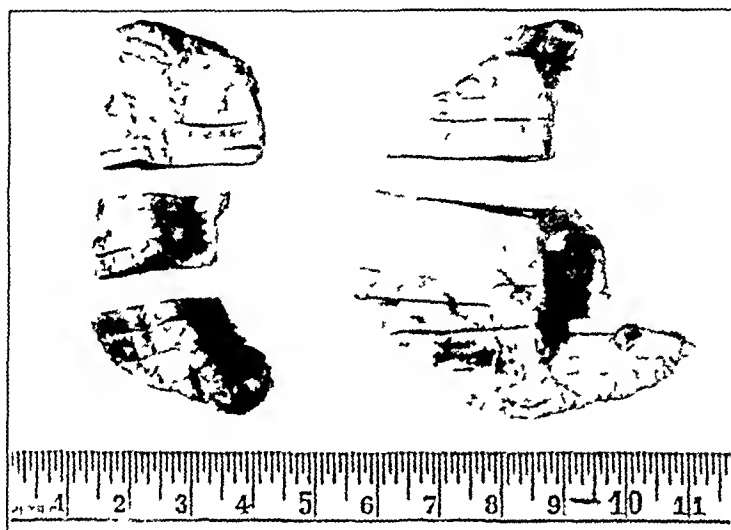


Fig 8 (L. G. H.)—Diffuse bilateral hypertrophy of the adrenal glands (weight, 21 Gm.)

*Cortical Neoplasms*—A cortical adenoma, varying in size from a few millimeters to 1 or 2 cm. is the neoplasm most frequently observed in the adrenal glands. In the majority of cases it gives no clinical evidence of its presence.<sup>7</sup> The frequency of the occurrence of such a small benign growth is borne out by a glance at the table. In none of the cases did the neoplasms produce clinical manifestations, it was observed incidentally at autopsy. Death resulted from arteriosclerotic heart disease in most of these cases. The average size of the adenomas was 1 cm., and the largest one measured 4 by 2 cm. (fig 9). All the adenomas were composed of cortical cells arranged in a somewhat disorderly fashion.

<sup>17</sup> Mackay, E. M., and Mackay, L. L. Compensatory Hypertrophy of the Adrenal Cortex, *J. Exper. Med.* **43** 395, 1926.

A malignant growth of the adrenal cortex as a rule has a rapid and fatal course. Such a growth occurs more frequently in women than in men, and changes in the secondary sexual characteristics are often the only signs present, but even these may be absent, this is especially true in men. An Addisonian syndrome is very uncommon.

The carcinoma of the adrenal cortex here described occurred in a 53 year old man (B. L.). The large number of infectious diseases in his past history is of some import. He had had typhoid at 12 years of age and rheumatic fever at 16. A gonorrheal infection occurred at 18, with a recurrence at 35 years. Tonsillectomy was done at the age of 46 because of frequent recurrent attacks of tonsillitis and severe cervical arthritis. Eight months before death he first complained of cough, with the production of purulent material and some loss in weight. Roentgeno-

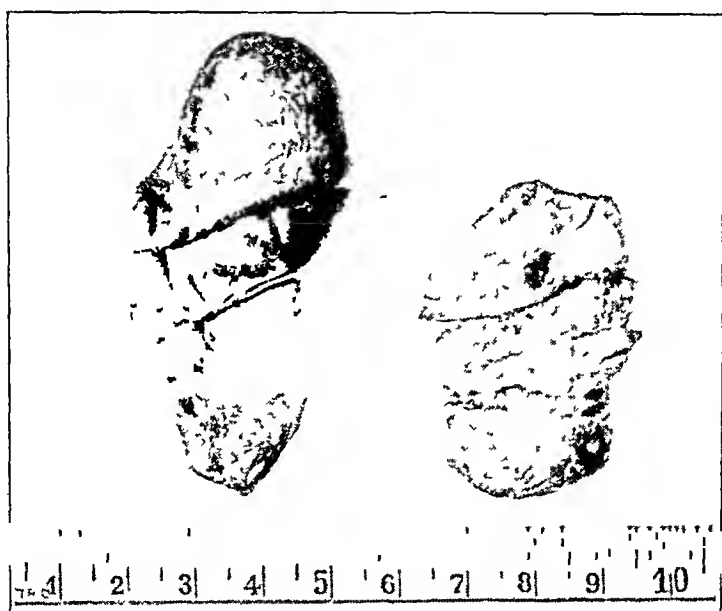


Fig. 9 (C. McM.)—Cortical adenoma of the right adrenal gland. Hypertrophy of the trunk and upper extremities was the only evidence of possible hyperadrenia.

grams gave evidence of healed apical tuberculosis and a small mass in the mediastinum. Twinges of pain in the left leg, which soon developed into well established radiculitis of the lumbosacral plexus, developed five months before death. A clinical diagnosis of generalized carcinomatosis with metastases to the spine and with pressure on the nerve roots was made. Careful examination failed to reveal the site of the primary growth. Irradiation over the mediastinal region brought about some betterment in the cough but failed to cause any diminution in the tumor. Irradiation over the lumbar part of the spine caused no perceptible improvement. Chordotomy in the upper part of the thoracic region on the right was done two months after the onset of the radiculitis in the hope that it might relieve the patient of his pain. This was accomplished to some extent, but right-sided radiculitis developed one month later. The patient became extremely cachectic and died about eight months after the onset of the clinical symptoms.

At the autopsy the tracheobronchial lymph nodes were enlarged and contained firm gray-white tumor nodules, one of these compressed the right main bronchus. Large nodes in the upper and supero-anterior parts of the mediastinum were adherent to each other and projected into the upper part of the right pleural cavity. The retroperitoneal and inguinal nodes were large and similar to those in the mediastinum and about the lungs. The peritoneum was dotted here and there with tumor nodules, the largest one was in the serosa at the junction of the rectum and the sigmoid flexure. There were nodules in the liver and kidneys. The adrenal glands were at least twice the normal size, and surfaces made by cutting were streaked with gray, firm tumor masses and isolated small islands of yellowish tissue. Microscopically, there were a few islands of cortical cells filled with lipid. These were surrounded by a tumor composed of columns and small masses of large atypical cells. The latter resembled more or less cells of the

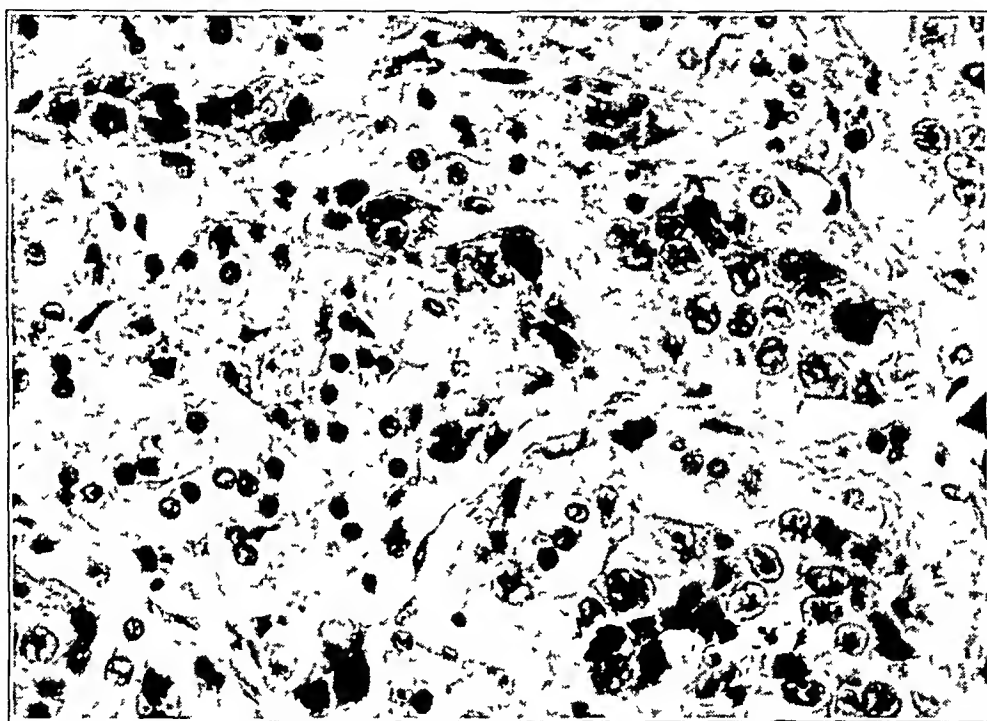


Fig 10 (B L) —Photomicrograph of primary carcinoma of the adrenal glands. The multicentric origin of the tumor is evident, and transitional stages between cortical cells and the tumor may be seen.

adrenal cortex. The tumor cells were supported in places by heavy fibrous stroma and in others by a delicate reticulum. Some of the tumor cells were multinucleated, and others had many mitoses. There was invasion by tumor cells of the capsule and periadrenal fat. In another section the three layers of adrenal cortex were distinguishable, but there were small masses of very large atypical cells in intimate association with the more normal-appearing cells of the adrenal cortex (fig 10). The blood sinuses were distended, and there were a few small hemorrhages. Small collections of lymphocytes were present in the deeper part of the cortex. The metastatic nodules were similar microscopically to the lesions in the adrenal glands. Terminal bronchopneumonia and fibrinopurulent pericarditis were the only other lesions observed in this body.



Early widespread metastasis and marked cachexia occur frequently in association with adrenal carcinoma. The metastatic lesions often produce the first clinical manifestations of disease<sup>18</sup>. In the case reported here the first symptoms were occasioned by the growths in the tracheobronchial lymph nodes and mediastinum, followed a short time afterward by radiculitis secondary to metastases in the retroperitoneal lymph nodes.

#### COMMENT

The rather high incidence (12.8 per cent) of adrenal hemorrhage in the adult is noteworthy in this series of 39 records of cases. In 2 persons the hemorrhage was massive and occurred during the course of an acute infectious disease. Clinical signs of adrenal insufficiency were present in only 1 instance (D F R). In 2 other cases hemorrhage of moderate degree occurred in the adrenal glands as a terminal complication (in a case of carcinoma of the prostate and in 1 of myelogenous leukemia). Routine examination of the adrenal glands at post-mortem examination has in recent years increased the number of recorded cases of adrenal hemorrhage in the adult.

There is liability to sudden death, spontaneous or postoperative, in chronic adrenal insufficiency. Death may be sudden and unforeseen, as in the case of P C T, but is most likely to happen when there is a sudden demand for increased adrenal function. This is well illustrated in 5 cases (those of M C, J S, M L, T M and A H). It is probable that life could have been prolonged in 4 of these (those of M C, M L, T M and A H) if the operation had been deferred or modified. In each of these patients there were signs and symptoms suggestive of chronic adrenal dysfunction. It is evident from an analysis of these records that there is need of additional criteria in establishing the presence of adrenal lesions in the living patient. Not infrequently hypotension or other signs which the physician associates with hypoadrenia may be found during the course of a physical examination in persons who come to the physician with some ailment requiring surgical intervention. Careful investigation of this group of patients, the idea of adrenal insufficiency being kept in mind, may elicit additional corroborative data. Repeated blood pressure readings are also suggested. If operation becomes imperative it would be well for the surgeon to acquaint the relatives of the possibility of an unfortunate outcome.

Injections of extract of adrenal cortex, accompanied by the oral administration of a sodium salt, have a beneficial effect in Addison's disease. Response to such measures, and frequent blood pressure readings, may aid in the diagnosis in cases in which the symptoms are indefinite and pigmentation is absent.

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18 Meyer, J, and Frumess, G. Tumors of the Suprarenal Gland with Special Reference to Carcinoma of the Cortex, *Arch Int Med* 48:611 (Oct) 1931.

# THE ETIOLOGIC SIGNIFICANCE OF STREPTOCOCCI IN EPIDEMIC ENCEPHALITIS

## II EXPERIMENTS WITH ANIMALS AND CONCLUSIONS

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In a previous paper <sup>1</sup> we described the biologic properties of the streptococci obtained from patients with encephalitis, their agglutination reactions with Rosenow's encephalitis antistreptococcus serum and their cataphoretic velocity and compared these data with those obtained by a parallel study of similar cultures from normal persons residing in St Louis, as well as in a locality far removed from the area of the epidemic. It is the purpose of this communication to describe the results which followed intracerebral inoculation of the cultures obtained from patients and from normal persons into animals and our experiments bearing on the immunologic relationship of the streptococci isolated to clinical encephalitis.

### TECHNIC

As in the previously reported work we were at particular pains in the experiments with animals to follow in all essential details the procedures used by Dr Rosenow, who was kind enough to give us a full personal demonstration. Dr Rosenow in our laboratory inoculated four rabbits with a strain of Streptococcus which he had freshly isolated from a patient with encephalitis in St Louis. The following day he performed autopsies on the two rabbits that had died. He later observed rabbits inoculated by us and gave us further advice on dosage and other details.

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1 Burdon, K L, Thurston, E W, Varney, P L, and Bronfenbrenner, J. The Etiologic Significance of Streptococci in Epidemic Encephalitis. I. Incidence of Streptococci in Cultures from Patients with Encephalitis in St Louis and from Normal Controls, and Characteristics of the Various Strains Isolated, Arch Int Med **58** 285 (Aug) 1936.

The procedures followed in our work with animals are outlined in the following paragraphs

*Inoculation of Animals*—The primary brain broth cultures were inoculated intracerebrally into rabbits in doses of from 0.1 to 0.2 cc of a 1:10, 1:100 or 1:1,000 dilution of the eighteen to twenty-four hour old culture in broth. In the majority of cases only the smallest dose (0.1 cc of the 1:1,000 dilution) was used. Pure cultures of the streptococci were inoculated in a dilution of 1:1,000 in all experiments. Albino rabbits were used almost exclusively, ranging in weight from approximately 1,500 to 2,500 Gm. Before inoculation the animals were anesthetized, the hair over the head was clipped, and the exposed surface was thoroughly disinfected with acetone. An incision about 1 inch (2.5 cm) in length was made in the sterilized area of the skin at about the midline, the skin was held apart, exposing the skull, and was moved a little to the left of the median line. There, at the level of the posterior angle of the eyes, a hole was drilled through the skull by means of a fine steel point, which was equipped with a guard preventing it from penetrating beyond a depth of  $\frac{1}{8}$  inch (0.3 cm). The inoculating needle was inserted through this opening and into the brain to a depth of about  $\frac{3}{8}$  inch (0.9 cm), withdrawn gradually as the material was injected and finally removed slowly, so as to avoid any loss of the inoculum. The incised skin was brought together and sealed with collodion. Care was exercised to maintain the uniformity of this procedure throughout all experiments. As a check on the nature of the actual material inoculated, a portion of the inoculum was always streaked on blood agar plates immediately after the injection.

*Symptoms and Postmortem Observations*—Inoculated animals were watched carefully and frequently were removed from their cages for closer observation and recording of symptoms. In some instances they were photographed by a moving picture camera, and in this manner a permanent record of their behavior in various stages of illness was secured.

Autopsies were performed as soon as possible after death. The entire body of the rabbit was first wet with dilute disinfectant. The skull was opened aseptically, and cultures were made from the ventricular fluid and the brain substance, the material being secured by means of sterile capillary pipets and inoculated directly into tubes of warm dextrose-brain broth and streaked over warm blood agar plates. Usually a direct smear was made from the meninges at the base of the brain or from the spinal fluid in order to determine the character of the exudate if any was present. The chest was then immediately opened, and through the seared surface of the heart from 0.2 to 0.5 cc of blood was obtained and inoculated into warmed dextrose-brain broth and onto blood agar plates. The brain, medulla and cervical portion of the cord as well as the other principal organs were examined for gross changes, then pieces of tissue from them were fixed in Zenker's acetic acid fixative, and in some instances additional pieces were fixed in formaldehyde. Sections from the tissues prepared with Zenker's fixative were stained by hematoxylin and eosin for study of the microscopic lesions, and the formaldehyde-fixed sections were stained by a modified Gram stain for the demonstration of bacteria.

The cultures in dextrose-brain broth inoculated with the material from the brain were transferred within twelve hours to new (warmed) tubes of the same medium and were maintained thereafter, so long as they were under study, by frequent transplants in the brain broth (from three to six transfers each twenty-four hours). These transfers were always made by removing with a

pipet a portion of the growth from the bottom of the column of broth near the brain substance and depositing this in a similar place near the brain material in the new tube, as recommended by Rosenow

RESULTS OF INOCULATION OF ANIMALS WITH CULTURES OF STREPTOCOCCI FROM PATIENTS WITH ENCEPHALITIS SELECTED  
AS TYPICAL BY DR ROSENOW

*Rabbits Inoculated in Our Laboratory by Dr Rosenow*—Four animals (two albino and two black and tan) were inoculated by Dr Rosenow personally in our laboratory

The inoculum used by Dr Rosenow was a passage strain of green colony streptococci cultured by him on the previous day from the brain of a rabbit which had died after intracerebral injection of the primary dextrose-brain broth culture of material from the nasopharynx of a patient in St Louis with acute encephalitis. One albino and one black and tan rabbit were inoculated intracerebrally with a growth of this strain in dextrose-brain broth approximately eighteen hours old, representing the second culture in the medium, and the other pair of rabbits (one albino and one black and tan) were inoculated in an identical manner with a younger growth (about ten hours old) of the same strain in its third transfer in the brain medium. In each case the inoculum consisted of 0.1 cc of a 1:1,000 dilution of the broth culture.

*Clinical Symptoms*—Within six hours both albino rabbits exhibited marked respiratory embarrassment and weakness of the limbs, especially the forelegs. They crouched in their cages with the ears back, breathing rapidly and noisily, and each labored breath was accompanied by trembling of the head and the forepart of the body. The rabbit which had received the younger culture showed the more severe symptoms at that time. In twelve hours this animal lay prone in the cage, breathing rapidly, with a gasping or grunting sound which could be heard across the room. When placed on its feet outside the cage, it could maintain its balance with difficulty and would not move unless prodded. It then staggered a few feet only and always in a circle toward the left ("cerebellar gait"<sup>2</sup>). The legs showed marked weakness, especially the forelegs, which tended to spread apart. The head bobbed up and down and weaved about, back and forth ("choreiform movements"<sup>2</sup>). It died approximately twenty hours after inoculation.

The other albino rabbit did not show acute illness quite as rapidly and twelve hours after the inoculation it was still able to move about, though it was obviously weak and showed gradually increasing difficulty in respiration. At the expiration of twenty-one hours it lay on its side, breathing with marked effort, too weak to do more than raise its head momentarily. While being watched it suddenly went into repeated convulsions and died in about fifteen minutes. At death the body was in rigid extension, with the hindlegs stretched backward and the head retracted.

As had been predicted by Dr Rosenow, the two black and tan rabbits inoculated at the same time and with the same material as the albino rabbits proved

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<sup>2</sup> The terms "cerebellar gait" and "choreiform movements" were suggested by Dr Rosenow as appropriate in describing the symptoms exhibited by this rabbit and when used in this paper they refer to the behavior described here.

to be distinctly more resistant than the latter. The animal receiving the eighteen hour old culture showed no definite symptoms for twenty-four hours. At that time there were present a slight unsteadiness in walking, a reluctance to move and a slight trembling of the forepart of the body. During the second day these symptoms became somewhat more pronounced, and, in addition, there was present a marked edema of the eyes and lacrimation. Respiration was somewhat rapid and irregular but not particularly labored. This condition continued practically unchanged until the third day, when convulsions suddenly developed and the rabbit died, fifty-one hours after the inoculation.

The other black and tan rabbit likewise did not appear definitely ill until about twenty-four hours after the inoculation and at first showed only a slight ataxia, trembling and edema of the eyes. Very severe convulsions soon occurred, however, following one another rapidly, while in the brief intervals between the animal lay on its side with the head and neck extended, gasping for breath. These convulsions continued at intervals of a few minutes for about two hours, then during the next five hours they became gradually less frequent and less severe, and eventually the animal was able to regain its feet after each seizure. The head was in almost continuous motion, weaving back and forth, but occasionally it came to rest sharply retracted, so that it was almost perpendicular to the neck. The eyes showed extreme edema. During the next three days the conjunctivae became opaque and there was marked nystagmus, but otherwise the general condition of the animal gradually improved. Convulsions still occurred occasionally but were less violent, and for considerable intervals the rabbit sat quiet, although the slightest stimulus, such as a sudden noise made by clapping of the hands, would cause the choreiform movements of the head to begin over again. A week after the inoculation the animal had a normal appetite, the eyes had returned to a normal condition, and the generalized convulsions no longer occurred. A mild degree of ataxia and the peculiar movements of the head with occasional sharp retraction or drooping continued, however, and this abnormal behavior persisted during the succeeding seven months during which the animal was observed<sup>3</sup> (fig 1 A).

The symptoms elicited in the albino rabbits as described were regarded by Dr. Rosenow as demonstrating the typical effects of "encephalitis" streptococci. Soon after the death of these rabbits autopsies were performed by Dr. Rosenow, and the notes on the gross changes observed at the time are given here. Additional comments made by Dr. Rosenow are indicated in parentheses.

Autopsy reports on the rabbits follow.

RABBIT 374—(Albino rabbit inoculated with the ten hour old culture of Rosenow's strain 302 in its third transfer.)

3 The relatively greater resistance of black and tan rabbits over the albino rabbits noted in this experiment seems to be real and not accidental, since we observed it again when we purposely inoculated one rabbit of each kind with the identical dose of a primary culture from the nasopharynx. The albino rabbit died in less than twenty-four hours, while the black and tan rabbit survived, though mild ataxia and peculiar choreiform movements of the head persisted for more than two months thereafter.

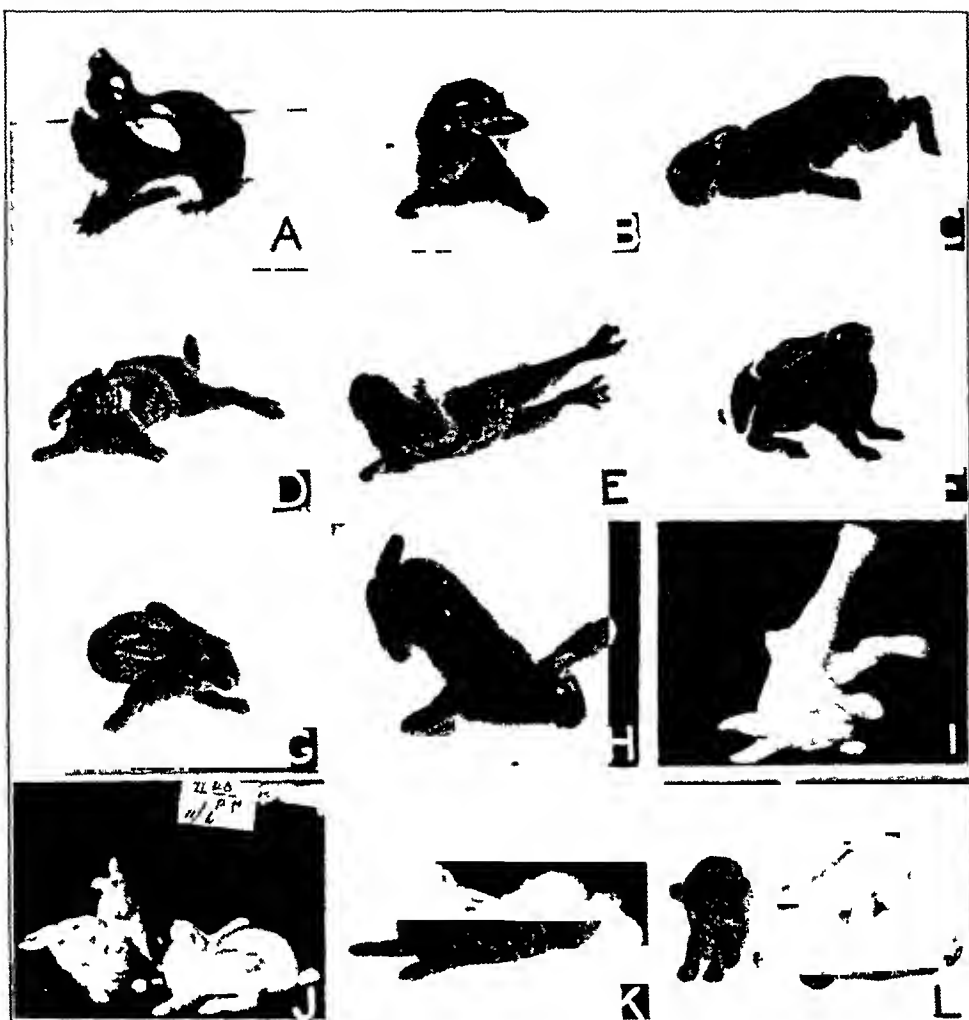


Fig 1—*A*, black and tan rabbit inoculated in our laboratory by Dr Rosenow with a pure culture of streptococci isolated by him on the previous day from the brain of a rabbit which had died after intracerebral injection of the primary nasopharyngeal culture from a patient with encephalitis in St Louis, showing the position often assumed by the animal during the acute illness and at intervals for many weeks after the inoculation *B* early stage of illness (about sixteen hours after inoculation) in a rabbit inoculated with a pure culture of green colony streptococci (passage strain En 24) isolated by us from a patient with encephalitis *C*, same rabbit as in *B*, shortly before death *D*, a rabbit inoculated with a pure culture of streptococci (passage strain En 29) originating from a patient with encephalitis, about twenty-four hours after the inoculation *E*, same rabbit as *D*, showing convulsive movement in late stage of the illness *F*, *G*, *H* and *I*, progressive stages of illness in a rabbit receiving intracerebrally a mixture of a pure culture of streptococci (passage strain En 29) and human encephalitic convalescent serum (note the similarity to those rabbits [*D* and *E*] receiving the culture alone) *J*, three of the rabbits used in a protection experiment, photographed about twenty-four hours after the inoculations, the animals (left to right) received, respectively, a mixture of a culture of streptococci (passage strain En 29) and normal horse serum, the same culture alone and the same culture mixed with human encephalitis convalescent serum *K*, opisthotonos in a rabbit injected with a mixture of a streptococcus culture (passage strain En 29) and Rosenow's encephalitis anti-streptococcus serum, photographed fifty hours after inoculation *L*, a group of rabbits in a protection experiment twenty-four hours after inoculation, the animal at the left received a mixture of a pure streptococcus culture (passage strain En 29) and human encephalitis convalescent serum, the animal in the foreground received the same culture alone, the animal in the rear received this culture mixed with Rosenow's encephalitis antistreptococcus serum (the latter rabbit shows practically no symptoms) All photographs are enlargements from a motion picture film

**External Appearance** The animal was in rigid extension. Little rigor mortis was present (common finding). Extreme congestion of the veins of the ear was present.

**Eyes** Extreme edema of the conjunctivae was present, and there were several petechiae in the circumcorneal areas. (The changes of the eyes probably are the counterpart of those responsible for ocular symptoms in human patients with encephalitis.)

**Brain** Slight cloudiness of the meninges and of the cerebrospinal fluid was noted (in this case there was more gross meningitis than is usually seen in inoculated rabbits). A small hemorrhage was present at the site of inoculation only. (No abscess is ever seen at the site of inoculation.) No petechiae or pink tinge was observed in the arachnoid. The brain showed only a moderate degree of softening and congestion of the cerebral vessels.

**Thoracic Organs** The trachea was congested and hemorrhagic, especially in the lower half. The lungs showed marked hemorrhagic edema of all the lobes. (The lesions of the lungs and the trachea were almost identical with those seen in rabbits dying after intracerebral injection of "influenza" strains of streptococci.) The heart showed extreme contraction of the left ventricle (often noted). Numerous subepicardial petechiae were present over both the right and the left ventricle, and subendocardial hemorrhages were noted, several extending into the base of the valves. The myocardium showed marked cloudy swelling and appeared cyanotic and gray. (These changes are not seen in rabbits dying after injection of "poliomyelitis" strains of streptococci.)

**Abdominal Organs** The spleen was slightly softened, the liver showed marked cloudy swelling and the kidneys showed swelling, with moderate edema and congestion and slight cyanosis.

**RABBIT 378**—(Albino rabbit inoculated with the eighteen hour old culture of Rosenow's strain 302 in its second transfer.)

**External Appearance** The forelimbs and hindlimbs were fully extended, some stiffness of the back was noted. The veins of the ear were markedly dilated.

**Eyes** The conjunctivae were edematous. Subconjunctival circumcorneal petechiae were present in the left eye.

**Brain** The meninges were smooth and shining, without any cloudiness. There was a slight increase in the amount of spinal fluid. Moderate congestion was present in the vessels of the medulla and of the anterior lobes, but there were no petechiae. No lesion was noted at the site of inoculation.

**Thoracic Organs** The trachea was markedly congested and hemorrhagic. Several subpleural hemorrhages were noted in both the right and the left lung, with no change in the pulmonary tissue proper. The heart showed much less congestion of the pericardial vessels than usual. Several subepicardial petechiae were present over the left ventricle, and there were numerous subendocardial petechiae in both ventricles, some extending into the valves. (These lesions were less severe than those observed in rabbits previously inoculated by Rosenow with cultures from patients in St. Louis.)

**Abdominal Organs** The spleen was swollen, soft and cyanotic (acute splenitis). The adrenal glands were normal (they almost never show gross changes). Cloudy swelling was present in the liver. The kidneys were slightly cyanotic (mulberry color) and swollen, the cortex was gray. The markings were conspicuous, and there was a marked congestion at the corticomedullary junction. (Changes in the kidneys may be due to toxin or may be secondary to pulmonary lesions, in this case the lungs were normal. The mulberry color

of the kidney is very typical and seems to be a change peculiar to and characteristic of the disease produced in rabbits by the St Louis strains of the encephalitis streptococcus<sup>4</sup>)

**Pathologic Changes in the Brain** Sections of the brain tissue from one of these albino rabbits and from the black and tan rabbit that died as well as from two other albino rabbits inoculated by Dr Rosenow elsewhere in St Louis with cultures from patients with encephalitis were available to us for microscopic study. In the sections from each of the four animals there was noted an infiltration of the pia-arachnoid by a mixture of polymorphonuclear leukocytes and large lymphocytes (fig 2 A and C). In three of these instances an exudate containing mostly polymorphonuclear cells was present in the ventricular cavities. The vessels of the arachnoid were dilated, and occasionally small hemorrhages were seen. In two instances the peripheral vessels—those arising in the pia-arachnoid and extending into the subjacent brain tissue—were surrounded by cuffs consisting of both polymorphonuclear leukocytes and large lymphocytes (fig 2 A and D). Cells of the same kind were also seen diffusely scattered in the upper layers of the cortex and in the subependymal tissue. Perivascular cuffing with round cells only, so characteristic of the lesions of encephalitis in human patients,<sup>5</sup> was not observed, and such perivascular infiltration as was noted appeared only in the superficial layers of the brain. Changes in the nerve elements, such as chromatolysis, loss of Nissl bodies and neuronophagy, were not observed. In brief, the main changes were those of purulent meningitis. Diplostreptococci were stained in the pia-arachnoid in three cases and also in one case in the superficial layers of the subependymal tissue near areas in which the continuity of the ependymal lining had been interrupted (fig 2 E).

*Rabbits Inoculated by Us with Strains of Encephalitis Streptococci Isolated by Dr Rosenow*—Further data on the type of symptoms and pathologic changes to be expected in rabbits inoculated with green colony streptococci from patients with encephalitis were secured by us when we later inoculated fourteen other albino rabbits with two different strains of encephalitis streptococci sent to us from Rochester by Dr Rosenow. Both strains had been isolated by him shortly before from the throats of patients with encephalitis in St Louis. One of them (strain no 7777<sup>3</sup> R7436 Br), which we designated Ros 2, represented the third animal passage of that strain, and the other (strain no 8231<sup>2</sup> R7424 Br), which we designated Ros 3, was in its second animal passage when received by us.

The strain Ros 2 was at once passed through two rabbits in succession, thus taking it through the fifth animal passage. The strain Ros 3 was carried through five consecutive passages, the final inoculation thus representing the

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4 Later, after he had had further opportunity to observe rabbits inoculated with material from patients in St Louis, Dr Rosenow informed us in personal conversation that he had not found the changes of the kidneys so constant or so characteristic as he had at first believed them to be.

5 McCordock, H A, Collier, W, and Gray, S H. The Pathologic Changes of the St Louis Type of Acute Encephalitis, J A M A **103** 822 (Sept 15) 1934.



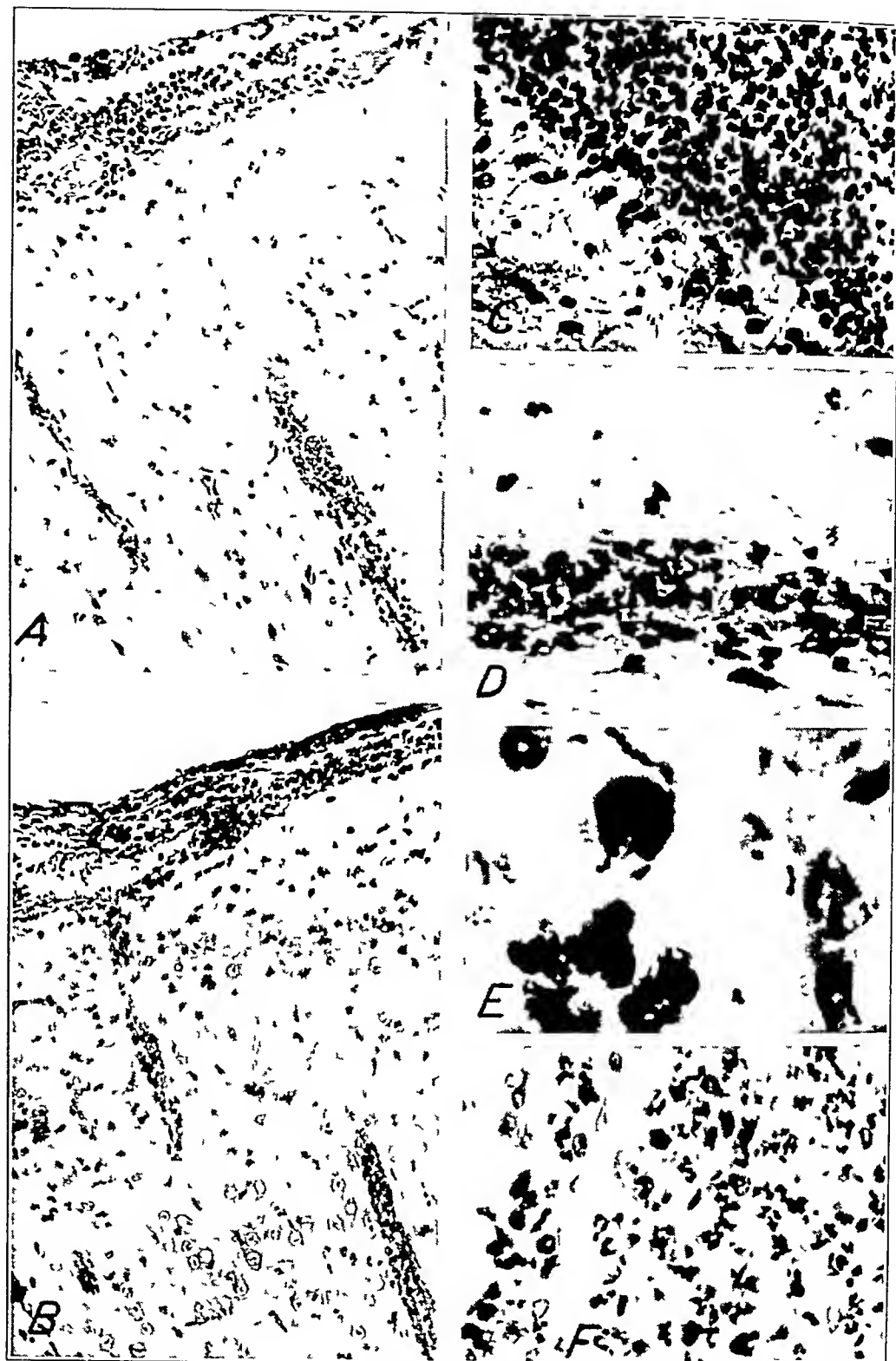


Fig 2—*A*, section of the cerebral cortex of an albino rabbit inoculated in our laboratory by Dr Rosenow with a culture of green colony streptococci isolated by him from a patient with encephalitis in St Louis *B*, a section of the cerebral cortex of a rabbit inoculated by us with a pure culture of streptococci isolated from a patient with encephalitis (note infiltration with polymorphonuclear and mononuclear cells in the meninges and the parenchyma, and about the superficial vessels, as in *A*) *C*, purulent meningeal exudate in a rabbit inoculated with one of Rosenow's strains of "encephalitis streptococci" *D*, enlargement to show the character of the perivascular infiltration in *A* *E*, exudate in the ventricular cavity of an inoculated rabbit, showing the streptococci *F*, purulent exudate in the meninges of a rabbit inoculated by us with the primary culture from the nasopharynx of a patient acutely ill with encephalitis

seventh animal passage for this strain. A total of twelve rabbits were inoculated with the strain Ros 3, groups of several animals receiving the identical culture at the same time. This was done in order to ascertain to what extent the progress of the infection may vary in individual rabbits inoculated with the same material. All the animals—those inoculated with strain Ros 2, as well as those receiving the Ros 3 strain—died, the majority in less than twenty-four hours.

The symptoms in all these rabbits were fairly uniform and similar to those observed in the two albino rabbits inoculated by Dr. Rosenow, already described. The percentage incidence of the principal symptoms in all the sixteen albino rabbits inoculated with Rosenow's strains is given in table 1.

The first signs of illness were apparent in most of the animals within from eight to ten hours after the inoculation. In a few cases the early symptoms of mild ataxia, reluctance to move voluntarily and moderate dyspnea persisted without any apparent advance in severity for ten or twelve hours before acute illness developed, but usually the symptoms became progressively more grave from their first appearance until death. It could not be said that the animals were lethargic at any time. On the contrary, in the early stages of the illness they were unusually excitable. Choreiform movements of the head were always observed early, and in the majority of instances the head when at rest became more and more strongly retracted. The neck and head were often twisted sharply to the right or left. Exceptionally the head dropped forward and came to rest continuously on the floor. About half the rabbits acquired a marked edema of the circumconjunctival tissues, a smaller proportion showed nystagmus.

One of the first signs noted was the weakness of the legs, which tended to buckle under when the weight was on them. Usually the forelegs eventually spread wide apart, and the animal was unable to hold them together despite all effort to do so. The hindlegs, on the contrary, were not greatly weakened and rarely became paralyzed. At the time when the symptoms were well developed, the rabbits appeared dazed and disoriented and if prodded would stagger dizzily in a circular path, turning always in the same direction. Later the animals fell on the side, and while at first they were able to regain a sitting position by violent effort, they could not maintain it and eventually they could no longer rise at all. In all the rabbits gross tremors of various muscles all over the body were observed. Generalized convulsions were not the rule, but in the final stage more than half the rabbits had involuntary spasmodic movements of large groups of muscles, which we often reported as convulsions. About a third of the animals collapsed on the side rather early in the course of the illness and remained thus for a protracted period before death, during which time there was observed a very slow sinking of their vitality.

In the majority of the rabbits severe dyspnea existed throughout the illness, and there usually developed a purulent discharge from the nose in which gram-positive diplococci were demonstrable microscopically. In the few animals in which the respiratory embarrassment was relatively slight, the symptoms were less acute, and in general the degree of involvement of the respiratory system was apparently more closely correlated with the severity of the illness and the time of death than with any other factor.

It is to be especially noted that, although the illness in all the rabbits followed a fairly uniform and to a certain degree predictable course, there was considerable variation in the prominence with which different symptoms, such as the tremors of the body, movements of the head or abnormal postures, developed in different rabbits, and these variations were as marked among the individual animals in the

TABLE 1—Incidence of Symptoms and Mortality in Rabbits Inoculated Intracerebrally with Cultures Containing Green Colony Streptococci from Patients with Encephalitis and from Normal Persons in St Louis and Washington D C

		Number and Percentage of Rabbits Showing Particular Symptoms																									
Inoculum	Total Number of Strains	Total Number of Albino Rabbits Inoculated	Symptoms														Mortality		Green Colony Streptococci Recovered at Autopsy								
			Ataxia Cerebral Gait	Dyspnea	Choreiform Movements of Head	Drooping of Head	Retracted Head	Head Twisted to One Side	Edema of Eyes	Nystagmus	Forelegs Weakened, Spread Apart	Hindlegs Paralyzed	Legs Extended at Death	Tremors of Body	Convulsions	Protracted Collapse Before Death	No Symptoms	Symptoms, with Recovery	Total Percentage of Total Number Inoculated	Percentage Dying in 48 Hours or Less	From Brain	From Heart Blood					
Pure cultures of encephalitis streptococci isolated by Rosenow	3	16	Total observed	12	13	12	16	16	16	14	12	13	12	16	11	11	16	0	0	16	100	75	10	0	9	9	0
			No showing symptom	12	13	12	2	11	7	6	2	13	1	12	11	6	5	0	0	0	16	100	75	10	0	5	0
			Percentage incidence	100	100	100	12	69	44	13	17	100	8	75	100	54	31	0	0	100	0	56	0	0	56	0	
Unpurified primary cultures from the nasopharynxes of patients with encephalitis in St Louis	21	23	Total observed	15	18	14	19	19	19	12	12	16	19	18	14	14	18	1	1	18	78	72	15	15	14	14	14
			No showing symptom	15	18	14	6	15	9	8	2	16	2	15	12	2	10	1	1	78	72	7	5	3	0	0	
			Percentage incidence	100	100	100	32	79	47	67	17	100	10	83	86	14	66	4	4	47	33	21	0	21	0	0	
Pure cultures of streptococci isolated by us from patients in St Louis	3	31	Total observed	28	29	25	31	31	31	29	28	28	28	30	27	25	31	0	0	31	100	84	15	15	5	5	5
			No showing symptom	28	29	24	10	28	15	19	4	28	10	20	27	4	4	0	0	31	100	84	15	15	0	2	0
			Percentage incidence	100	100	96	32	90	48	65	14	100	36	67	100	16	13	0	0	100	0	40	40	0	40	0	
Totals	27	70	Total observed	55	60	51	66	66	66	55	52	57	59	64	52	50	65	4	1	65	93	77					
			No showing symptom	55	60	50	18	54	31	33	8	57	47	50	12	19	4	4	1	65	93	77					
			Percentage incidence	100	100	98	27	82	47	60	15	100	22	73	96	24	29	4	1	93	77						
Unpurified primary cultures from the nasopharynxes of normal persons in St Louis	4	4	Total observed	3	3	2	3	3	3	2	2	3	3	3	1	1	3	1	0	3	75	100	3	3	3	3	3
			No showing symptom	3	3	2	2	1	0	1	0	3	2	1	1	1	1	1	0	3	75	100	2	1	0	1	
			Percentage incidence	100	100	100	67	33	0	50	0	100	67	33	100	100	33	1	0	100	67	33	0	67	33	0	33
Unpurified primary cultures from the nasopharynxes of normal persons in Washington, D C	6	6	Total observed	6	6	6	6	6	6	6	6	6	6	4	6	6	4	0	0	4	67	75	4	4	4	4	4
			No showing symptom	6	5	6	1	2	5	2	1	6	2	2	5	1	1	0	0	4	67	75	2	1	1	1	1
			Percentage incidence	100	83	100	17	33	83	33	17	100	33	50	83	17	25	0	0	100	67	75	50	25	25	25	25
Pure cultures of streptococci isolated by us from normal persons in St Louis and Washington, D C	6	6	Total observed	2	2	2	4	4	4	2	2	3	4	3	2	2	3	2	1	3	50	66	2	2	2	2	2
			No showing symptom	2	1	2	1	3	0	0	0	3	0	3	2	0	0	2	1	3	50	66	2	2	0	1	0
			Percentage incidence	100	50	100	25	75	0	0	0	100	0	100	100	0	0	2	1	100	66	50	100	0	50	0	0
Totals	16	16	Total observed	11	11	10	13	13	13	10	10	12	13	10	9	9	10	3	3	10	62	81					
			No showing symptom	11	9	10	4	6	5	3	1	12	1	6	8	2	2	3	1	62	81						
			Percentage incidence	100	82	100	31	46	38	30	10	100	31	60	89	22	20	3	3	81							

groups of rabbits receiving the identical culture at the same time as they were among the rabbits receiving comparable doses of different strains

At the autopsy of ten of these sixteen animals cultures were made from the brain. In all instances the culture yielded a pure growth of streptococci, as did also the cultures of blood from five of nine of the rabbits

The pathologic changes observed in the rabbits inoculated with strain Ros 2 and Ros 3 did not differ materially from those in the animals inoculated by Dr. Rosenow and described previously. In table 2 the percentage incidence of the principal pathologic findings in all the sixteen rabbits inoculated with Rosenow's cultures is given

Grossly, more than two thirds of the animals showed a marked engorgement of the vessels of the leptomeninges, especially about the base of the brain. In two instances the cortex had a definitely pinkish tinge. There was present a visible meningeal exudate in three instances (19 per cent). Small subarachnoid hemorrhages were present in about a third of the rabbits, and in about half of them there occurred hemorrhage into the brain substance. The latter, however, consisted merely of small petechiae about the site of injection, except in three instances in which apparently fresh hemorrhages of considerable size had occurred. Petechiae in the heart and in the pleura were each observed in about one fourth of the animals. Sixty-nine per cent of the rabbits showed hemorrhagic edema of some degree in the lungs. Slight congestion of the liver was noted in a few cases, and in the majority the spleen was found to be moderately swollen and softened. The kidneys were congested in some degree in all the animals, but there was nothing peculiar or characteristic about the appearance of these organs.

Microscopic examination of the brains of the rabbits of this group revealed essentially the same picture as was seen in the animals inoculated by Rosenow and described earlier. The majority of the rabbits showed the presence of a meningeal exudate as the most conspicuous feature. This exudate always consisted of a mixture of large lymphocytes and polymorphonuclear cells, which were present in various proportions in different parts of the same sections. Infiltrations of lymphocytes and polymorphonuclears were also observed about the superficial cortical vessels, but perivascular cuffing with round cells alone was not seen. No changes in the nerve cells were observed. The streptococci were readily demonstrable in the meningeal exudate and occasionally in the cortical parenchyma.

*Monkeys Inoculated with One of Rosenow's Strains*—Since in the early study of this epidemic the transmissibility of encephalitis to monkeys by intracerebral inoculation with a filtrable virus from the brains of patients with encephalitis had been established, it was deemed interesting to compare the symptoms and pathologic changes observed in these animals as the result of injection of the virus with those which might be produced by injection of the streptococci.

The relative insusceptibility of rhesus monkeys to intracerebral inoculation with green colony streptococci has been noted by several authors. Rosenow in his attempts to infect monkeys with his strains of streptococci isolated from patients with poliomyelitis and encephalitis usually adopted the procedure of giving repeated intracerebral inoculations (three or more) at intervals of a few days until some sort of symptoms were produced.

Number and Percentage of Rabbits Showing Particular Pathologic Changes

	Total Number of Autopsies	Gross Pathologic Findings										Microscopic Pathologic Observations																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																											
		Brain					Eyes					Heart					Lungs					Liver Spleen					Kidneys					Brain					Lungs					Liver Spleen					Kidneys																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																								
		Meningeal Exudate		Hemorrhage in Brain Substance		Subarachnoid Hemorrhage	Pinkness of Cortex		Circumcorneal Congestion or Hemorrhage		Conjunctival Edema	Subcardial, Epicardial or Endocardial Hemorrhages		Hemorrhagic Edema		Subpleural Hemorrhages		Congestion		Swelling, Softening		Purulent Meningitis		Hemorrhages in Parenchyma		Perivascular Infiltration		In Exudate		In Parenchyma		Edema		Bronchopneumonia		Cloudy Swelling																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																			

The strain Ros 3 was chosen for the inoculation of monkeys, since it was the most typical of those available. Not only was this strain capable of producing in rabbits the characteristic illness (as noted), but it was agglutinated in high dilution (1:10,240) by Rosenow's "encephalitis antistreptococcus serum" and subcultures showed frequently an average cataphoretic velocity approaching the "neurotropic" zone (i. e., a cataphoretic time of about 4 seconds). Just prior to the inoculation of the monkeys a culture of this strain was injected intracerebrally in the dose of 0.1 cc of a 1:1,000 dilution into an albino rabbit (fourth animal passage). This rabbit had the usual illness and died in about forty hours. The streptococci were cultured from the brain in dextrose-brain broth, and this culture, twelve hours old, was injected intracerebrally in the amount of 0.5 cc of a 1:100 dilution into a normal monkey. No sign of illness of any kind appeared as a result of this inoculation during several weeks in which the monkey was observed.

Two days later a second monkey was inoculated intracerebrally with the same strain, which had been passed in the meantime through many transfers in dextrose-brain broth medium. This monkey was given 1 cc of the undiluted culture—an extremely heavy inoculation. In order to test the nature of the relatively high resistance of monkeys to streptococci (as noted in the first monkey inoculated) this second monkey was bled just before it was inoculated, and a rabbit was inoculated intracerebrally with a mixture of an equal volume of the monkey's serum and a 1:500 dilution of the same culture. The mixture of the diluted culture and the normal monkey serum was allowed to stand at incubator temperature for one and one-half hours before it was inoculated intracerebrally into the rabbit. Another rabbit was inoculated at the same time with a 1:1,000 dilution of the identical culture (without serum) as a control.

Twelve hours after the inoculation the monkey was definitely ill. It crouched in the corner of the cage with the head down between the shoulders. It was hard to arouse, but a sufficiently sharp noise would cause it to raise the head and take a few steps. When let alone it would return immediately to a crouching attitude, shivering slightly from time to time. Coarse tremors of the forelimbs were occasionally seen. The head was sometimes held sharply retracted for a brief period. The left eye (on the side of inoculation) showed edema and ptosis of the lid. The right showed only a tendency to profuse lacrimation. These abnormalities lasted for only a few hours, however, and within twenty-four hours after the inoculation both eyes appeared normal and all other symptoms had almost disappeared. Before the next day the animal fully recovered, and no residual symptoms of any kind were noted during the following several weeks of observation.

In sharp contrast, the control rabbit receiving the same (though greatly diluted) culture had the usual acute illness and died in about eighteen hours. The rabbit inoculated with the mixture of the culture and monkey serum also showed typical symptoms and collapsed early but lingered in this state, barely alive, for three days. This result suggests that the normal monkey serum may possibly have had some slight protective effect.

#### RESULT OF INOCULATION OF ANIMALS WITH CULTURES OBTAINED BY US FROM PATIENTS WITH ENCEPHALITIS

*Primary Cultures from the Nasopharynx*—The primary dextrose-brain broth cultures from the nasopharynges of twenty-one patients with encephalitis were inoculated into a total of twenty-three albino rabbits.

The material for culture was obtained in the manner previously described<sup>1</sup> and was incubated about eighteen hours, and in no case for more than twenty-eight hours, before inoculation. The dose in all cases was 0.1 cc., intracerebrally, of a freshly made dilution in warm broth. Eight of the animals received the culture in a 1:10 dilution, four in a 1:100 dilution and eleven in a 1:1,000 dilution. Of the twenty-three rabbits thus inoculated, one showed only mild and transient symptoms followed by complete recovery, four showed no symptoms whatever, and eighteen (78 per cent) showed progressive illness and died. Of the eighteen deaths, thirteen (72 per cent) occurred within forty-eight hours after the inoculation and the remaining five in from three to five days (table 1).

The degree of dilution of the primary culture apparently was not the decisive factor in determining the final outcome of infection, since nine of the eleven rabbits receiving the least amount of culture (1:1,000 dilution) died, whereas one of the rabbits receiving a 1:100 dilution had transient symptoms only, and among the four animals which showed no symptoms at all, two received the largest amount (1:10 dilution) of the cultures.

At the time the nasopharyngeal swabbings were made, nineteen of the twenty-one patients were acutely ill and presented clinically typical encephalitis of from two to nine days' duration, one patient had mild and atypical symptoms only of nineteen days' duration, and one was convalescent after a typical attack of acute encephalitis three weeks earlier. No correlation could be made out between the clinical state of the individual patient from whose nasopharynx the cultures were obtained and the character and severity of the symptoms in the inoculated rabbits. The culture from the patient with a mild, atypical attack and also the one from the convalescent patient produced a fatal illness like that caused by other primary cultures from the nasopharynxes of the acutely ill. All the four rabbits that showed no symptoms received cultures from patients with typical acute encephalitis.

On the other hand, the results of the inoculation of the rabbits appeared to be definitely influenced by the relative number of green colony streptococci present in the injected material, as revealed by the control streaked blood agar plates made from each inoculum at the time of inoculation. These plates showed that the material injected in all cases was a mixture containing green colony streptococci and a variable proportion of other organisms, mainly staphylococci, except in two instances in which the inoculum consisted of an apparently pure culture of the streptococci. That the green colony streptococci in these cultures were principally responsible for the acute infection and death which occurred in most of the rabbits is clearly indicated by the somewhat milder illness that followed inoculation with certain of the primary cultures in which streptococci were comparatively few, as well as by the fact that cultures from the brains of the rabbits at autopsy yielded in many cases practically a pure growth of these streptococci.

Four animals received cultures in which staphylococci or other bacteria were apparently more numerous than the streptococci. In two of these rabbits the illness ran a slower and milder course than usual, and these two were the only rabbits of the entire group that survived as long as five days. No organisms were recovered from the brain of one of these animals, and from the other an almost pure growth of hemolytic staphylococci, accompanied by only a few colonies of green colony streptococci, was obtained. A third rabbit showed acute symptoms and died in about thirty hours, but in this case a heavy growth of green streptococci, mixed with a smaller number of hemolytic staphylococci, appeared in cultures from the brain. The fourth animal was among those showing no symptoms.

The three other rabbits that remained without symptoms, as well as the animal that had transient illness only, received cultures which contained apparently as many green colony streptococci as did most of the cultures that produced acute disease in other animals. These were among the earlier experiments, however, and it is believed that the failure to cause the usual illness might have been due to the escape of part of the inoculum from the skull after injection.

The predominance of green colony streptococci in the brains of those rabbits that died after intracerebral injection of the unpurified primary cultures from the nasopharynges of the patients with encephalitis was clearly shown in the cultures made at autopsy (table 1). Fifteen rabbits were examined bacteriologically. In three instances cultures from the brain in dextrose-brain broth yielded no growth, but in all the remaining twelve (80 per cent) the cultures from the brain contained green colony streptococci. These were distinctly more abundant than any other organism in nearly every instance, and in the case of seven of the animals (47 per cent) they were the only organisms found. It appears that when the green colony streptococci were sufficiently numerous in the original inoculum they multiplied freely in the brains of the inoculated animals and tended to crowd out the accompanying organisms. In contrast to the regularity of their presence in the brain, the streptococci were observed at autopsy in the blood of only three rabbits of the fourteen examined (21 per cent). These results are in accord with those reported after similar intracerebral inoculations of rabbits with mixed cultures from patients with diseases of the nervous system by Rosenow, and it is findings of this kind which are the basis of Rosenow's contention that these green colony streptococci exhibit neurotropic properties.

The symptoms observed in this group of rabbits receiving inoculations of primary cultures from the nasopharynges of patients with encephalitis closely resembled those in animals inoculated with the cultures of streptococci obtained from Dr Rosenow, as described earlier. The percentage incidence of the various symptoms was very nearly the same in the two groups of rabbits (table 1). In general, fewer of the animals given the primary cultures were observed in convulsions, a larger proportion died a lingering death after a protracted period of collapse and there was perhaps a somewhat greater variation in the character of symptoms in individual rabbits, but there were no significant or consistent differences in the course of the illness which would distinguish it from that produced by the injection of Rosenow's cultures.

As noted before, severe respiratory symptoms were associated with early death. It was impossible to predict correctly from the symptoms shown by a particular animal whether at autopsy the cultures from the brain would reveal the presence of streptococci only or a mixture of streptococci and other organisms. The prominence of certain symptoms in a particular animal (such as extreme torticollis, retraction of the head, marked nystagmus and edema of the eyes, or spasms of the diaphragm) could not be correlated in any case with the clinical history of the patient from whom the culture was obtained.

As with the symptoms, the pathologic changes (table 2) were not essentially different from those observed in the rabbits dying after the injection of cultures of streptococci received from Rosenow, and the description previously given would apply equally well here. Again, the only gross changes in the brain apparently consisted of a congestion of the cortical vessels. Six of the fifteen animals examined (40 per cent) had hemorrhagic edema, and four (27 per cent) showed subpleural hemorrhages. Congestion of the kidneys was observed in only seven instances, and there was nothing especially characteristic about this.



A meningeal exudate was noted grossly in only one case (cultures later showed the presence of many hemolytic staphylococci in the brain of this rabbit), but microscopic examination of sections from the brains of thirteen of the rabbits showed some degree of meningitis to be the most constant and conspicuous pathologic change in every case. A purulent meningeal exudate was especially marked in two animals, both of which had been inoculated with material containing many staphylococci. However, in other animals also (including those from which pure cultures of green colony streptococci were obtained from the brain at death and those dying at various times from sixteen to seventy hours after the inoculation), a more or less marked infiltration of the arachnoid with a mixture of large lymphocytes and polymorphonuclear cells was seen in practically every section through any region of the brain (2F). In those animals that had lived longest, the lymphocytes often predominated in the exudate, although the polymorphonuclear leukocytes were also abundant. Infiltrations of the same mixture of the cells were observed in the nerve tissue subjacent to the meninges, and there were occasional small areas of necrosis, with many polymorphonuclear cells in which gram-positive cocci could be stained, but all these lesions appeared to be due to an extension of the reaction from the meninges. Perivascular cuffing was observed in sections from only about half the animals, and when present it nearly always occurred about the superficial vessels only. Rarely a vessel was seen surrounded by a cuff made up exclusively of lymphocytes, but usually many polymorphonuclears, as well as lymphocytes, were present. Aside from an occasional swollen (edematous) ganglion cell, no changes were observed in the nerve elements.

*Passage Cultures*—Two pure strains of green colony streptococci, recovered from the brains of rabbits dying after inoculation with the primary cultures from the nasopharynges of patients with typical acute encephalitis were selected for further experiments. The rabbits which had been inoculated with the respective primary cultures (and from which these strains were recovered) had shown the symptoms and the pathologic changes which appeared to be most characteristic of this experimental infection of rabbits.

One strain (designated En 24) was passed through three rabbits in succession, so that the last rabbit received this strain in its fourth animal passage. Strain En 29 was put through five successive passages in rabbits but was injected each time in the same dose into several animals, giving a total of twenty-seven rabbits receiving this strain. Throughout the period during which these cultures of streptococci were under study, they were never permitted to grow in brain broth for more than twelve hours before transplantation to a new culture tube or injection into another rabbit. The animals were inoculated in all cases with 0.1 cc of a 1:1,000 dilution of a ten to twelve hour old dextrose-brain broth culture. All the thirty rabbits inoculated with these strains died, the great majority in forty-eight hours or less.

The illness in these animals followed the course already familiar in other rabbits inoculated earlier, and the outstanding clinical features were observed in most characteristic form. The percentage incidence of the various symptoms in this group of animals is almost identical with that observed in the rabbits inoculated with the primary cultures from the patients with encephalitis or with Rosenow's cultures (table 1). Neither strain En 24 nor strain En 29 produced severe respira-

tory symptoms, but this and other clinical features varied in degree from animal to animal as they did in previously inoculated groups of rabbits. When our detailed notes and cinematographic records of symptoms were compared, there seemed to be no room for doubt that these rabbits had the same disease as that produced with the strains of green colony streptococci from patients with encephalitis selected and pronounced typical by Dr. Rosenow (fig. 1 *B, C, D* and *E*).

The virulence of the organisms cultured and the character of the symptoms produced were not materially changed as a result of passage in animals. The three rabbits inoculated in series with strain En 24 showed almost identical behavior, and the death of each occurred at almost exactly the same hour after inoculation. Similarly, there were no consistent differences in the effects produced by the strain En 29 throughout the five successive passages in animals, and certainly there was no evidence of an increase in the severity of the symptoms, although some differences were noted in the frequency of certain individual pathologic changes. If anything, the symptoms seemed to be slightly less severe in the fourth and fifth passages, though death occurred after about the same interval.

It should be noted that the individual rabbits composing the groups of from five to eight animals which were inoculated at the same time with the same dose of the passage strain En 29 did not exhibit identical behavior and that certain symptoms were much more prominent in some of the rabbits than in others of the same group. The amount of retraction, drooping and twisting of the head, the intensity of the ocular symptoms, the appearance of paralysis in the hindlegs and the degree of respiratory difficulty all varied in different rabbits inoculated with the same material. The difference in intensity of particular symptoms among such rabbits was at least as great as any similar differences between rabbits inoculated with different strains.

Both the gross and the microscopic pathologic changes in the thirty rabbits inoculated with strain En 24 or En 29 were essentially of the same character as those seen in the rabbits inoculated with Rosenow's cultures (table 2). Hemorrhagic edema in the lungs occurred in 42 per cent of the animals. In the brain a moderate degree of meningitis and some perivascular infiltration of the superficial vessels, mostly with polymorphonuclear cells, was observed in all the animals examined (fig. 2 *B*). This meningitis appeared to be somewhat intensified with successive passage in animals, so that with strain En 29, for example, clouding of the meninges and spinal fluid was observed grossly in six of eight (75 per cent) of the rabbits receiving this material in its fifth passage, whereas only one of five (20 per cent) showed a visible meningeal exudate on the second passage of this strain. A similar increase in the meningeal reaction occurring as the result of repeated successive passages in animals has been noted by Rosenow.

At the autopsy of fourteen of the rabbits inoculated with strains En 24 and En 29 cultures from the brains of the animals yielded pure growths of green colony streptococci. These organisms were also present in the heart blood from two animals of the five from which the blood was cultured.

*Strain HB<sub>1</sub>-1, From the Brain of a Patient with Epidemic Encephalitis*—An apparently pure culture of green colony streptococci was obtained by us in dextrose-brain broth inoculated with ventricular fluid secured at the autopsy of a patient with encephalitis. In view of the origin of this culture (strain HBr-1) its effects in the rabbit are of special interest. The usual dose of a young (eighteen hour) growth in dextrose-brain broth of the freshly isolated organism (0.1 cc. of a 1:1,000 dilution administered intracerebrally) killed a rabbit in about twenty hours. The symptoms were first noticeable in about ten hours and were chiefly character-

ized by dyspnea of increasing severity, while trembling, ataxia and other symptoms of nervous disorder were present but less prominent

The brain of this rabbit showed grossly only a moderate engorgement of the cerebral vessels and otherwise no change. Microscopic examination revealed a marked exudation into the arachnoid and about the vessels, consisting almost entirely of polymorphonuclear leukocytes. Some infiltration of these cells was also noted in the nerve tissue subjacent to the meninges. Otherwise no changes were noted. There was present an advanced hemorrhagic edema in the lungs. A pure growth of green colony streptococci developed in cultures made from the brain of this rabbit after death, while the culture of the heart blood was sterile.

Thus, both the symptoms and the pathologic changes in this animal followed the pattern noted in other inoculated rabbits previously described, and nothing more or less distinctive or reminiscent of human encephalitis was noted.

#### RESULTS OF INOCULATION OF ANIMALS WITH CULTURES OBTAINED BY US FROM NORMAL PERSONS

*Primary Cultures from the Nasopharynx*—The primary cultures in dextrose-brain broth from the nasopharynges of ten normal persons (six of whom were residents not of St. Louis but of Washington, D. C.), were injected intracerebrally into albino rabbits in exactly the same manner as similar cultures from the nasopharynges of patients with encephalitis.

The dose in all cases was 0.1 cc. of a 1:1,000 dilution of the eighteen to twenty-four hour old culture in broth. One of the rabbits receiving a culture from a resident of St. Louis showed no symptoms whatever (possibly because of technical error in the inoculation). Two of the animals inoculated with cultures from persons in Washington, D. C., showed moderately severe respiratory and nervous symptoms, but after a few days they recovered completely, except for slight ataxia. The remaining seven rabbits—three receiving primary cultures from the nasopharynges of normal persons in St. Louis and four receiving similar primary cultures from residents of Washington, D. C.—died, making a total mortality of 70 per cent. One of these rabbits did not die for nearly five days, but all the others died in forty-eight hours or less.

The illness in these rabbits was of the same character as that seen in the animals inoculated similarly with primary cultures from the nasopharynges of patients with encephalitis. As may be seen by inspection of table 1, the percentage incidence of the principal symptoms did not vary in any significant way from that in the other groups of rabbits inoculated with material from persons with encephalitis. However, there did seem to be this difference: the symptoms in most of the animals appeared somewhat more slowly, and in the first eighteen to twenty-four hours after the inoculation they were noticeably milder. But, as already mentioned, the animals died at about the same time after inoculation (average forty hours). There was no consistent difference in the effects produced in the rabbits by inoculation with cultures from well persons in the zone of the epidemic (St. Louis) who might conceivably have been in contact with a patient with encephalitis or with a carrier and of those from healthy persons residing in Washington, D. C., where the possibility of such contact was practically nil.

It was again apparent that the green colony streptococci in the injected cultures played the principal role in causation of symptoms and death in the rabbits. The

particular primary cultures used for the inoculations were chosen from among other cultures from the nasopharynges of healthy persons because they appeared to contain considerable numbers of these streptococci. The blood agar plates made from each inoculum at the time of inoculation showed that green colony streptococci were present in all instances, but they were mixed with a greater variety of other organisms, including many more diphtheroid bacilli and staphylococci, than were usually present in the primary cultures from patients with encephalitis. It seems probable that this accounts in part for the somewhat slower and milder course of the infection and for the accentuation of the signs of meningeal irritation, such as the marked retraction of the head seen in several of the rabbits. At autopsy, green colony streptococci were recovered from the brains of six of the rabbits, four times in pure culture, and also from the heart blood in three instances.

*Passage Cultures*—Reinjection into rabbits apparently demonstrated that some of the passage strains of these green colony streptococci originating from normal throats were somewhat less virulent than the strains similarly obtained from the nasopharynges of patients.

Of the four such passage strains injected, two killed rabbits in the usual dose in less than twenty-four hours, a third strain produced the familiar symptoms but in moderate form and the animal lingered for fourteen days before it finally died, while the fourth strain caused no illness whatever.

It must be noted that, although some of these strains from normal throats appeared to be less virulent for rabbits than streptococci from patients with encephalitis, the character of the illness produced by any of them did not differ materially from that caused by the most typical of the "encephalitis" streptococci.

Furthermore, the pathologic changes in the rabbits receiving either the unpurified primary cultures or the passage cultures from normal throats were essentially identical with those previously described (table 2). Indeed, some sections of the brain showed more marked damage to the nerve tissue (proliferation of glia cells and perivascular infiltration, with lymphocytes predominating) than was seen in sections from the brains of rabbits inoculated with cultures from patients. The most consistent and conspicuous pathologic change, as before, was a meningeal exudate, mainly of a purulent type.

#### IMMUNOLOGIC RELATIONSHIP OF THE STREPTOCOCCI TO CLINICAL ENCEPHALITIS

*Agglutination Tests with Convalescent Serums*—Since in the preceding studies no clear or consistent differences could be made out (in either the clinical or the pathologic features) between the illness which followed the intracerebral inoculation of rabbits with streptococcus-containing material from patients with encephalitis and that which occurred when similar material from healthy persons was injected, further experiments were indicated.

With the view of discovering any specific immunologic relation of the streptococci isolated to clinical encephalitis we first made agglutination tests with convalescent serum.

In carrying out these tests a number of serums were especially chosen—four from patients from whom we had isolated streptococci possessing the characteristic virulence for rabbits, five from other convalescent patients and five from monkeys surviving an attack of the experimental virus encephalitis. All these serums had been shown by Smadel and Muckenfuss to possess distinct protective power against the virus in mice. In addition, as controls, specimens of serum from six normal persons were tested.

As test organisms we selected twelve pure strains of streptococci. Three of these were among those obtained from Dr. Rosenow, one strain was isolated from a normal throat and in preliminary tests was found to be strongly agglutinated by Rosenow's serum, and eight strains were chosen as typical of those isolated by us from patients with encephalitis. Among the latter were four strains secured from the very patients whose serums were to be tested. Also included was the strain HBr-1, which was isolated originally from the brain of a patient who died of encephalitis.

All the tests were performed at the same time, suspensions of the organisms prepared from young, actively growing brain broth cultures, diluted to the same density, being employed as antigens. The tubes were incubated for two hours at 37 C and then placed in the icebox overnight before the final reading.

No change in the appearance of the suspensions was detectable at the end of the two hour incubation period. After the suspension had stood overnight, an irregular ring of granular sediment formed at the bottom of some tubes, although the supernatant fluid remained uniformly clouded. That this sedimentation had no significance as an index of specific agglutination was clearly shown by the fact that the same strains showed a similar sediment in the control tubes which were set up with normal serums. Thus, these tests indicated the absence of any specific agglutinating power against the streptococci on the part of any of the convalescent serums.

*Protection Tests with Convalescent Serums and with Rosenow's "Encephalitis Antistreptococcus Serum"*—Obviously another means of investigating the question of the part played by streptococci in the causation of epidemic encephalitis was that of testing the power of convalescent serum to protect rabbits against typical encephalitis strains. This seemed all the more worth while since the encephalitis which was transmissible to mice by the injection of the St. Louis virus could be prevented by the simultaneous injection of convalescent serum.

Consequently a series of experiments were performed to test the protective power of the convalescent serum from human patients and also from monkeys inoculated experimentally with the virus. For control inoculations normal human serum and normal horse serum and Rosenow's encephalitis antistreptococcus serum, which, according to Rosenow, should have a specific protective effect against encephalitis streptococci, were used.

The cultures employed for the intracerebral inoculation of rabbits in these experiments were the passage strains of proved virulence En 29 and Ros 3. Mixtures consisting of equal parts of the various serums and the ten to twelve hour old dextrose-brain broth cultures, diluted 1:500, were allowed to stand at

room temperature for about two hours before injection as recommended by Rosenow. Blood agar plate cultures made as a routine at the time of injection showed that the mixtures in every instance contained a pure strain of living green colony streptococci. In a few instances the serums were injected intravenously, and an hour later the cultures in 1:1,000 dilution were injected intracerebrally.

One of the protocols, illustrating a typical experiment, is shown in table 3. The results shown in this protocol are typical of those observed in all similar experiments. The control inoculations (first three animals) showed that the culture was virulent, causing a characteristic illness, and that neither normal human serum nor normal horse serum modified in any way the course of the infection in the rabbits. Rosenow's serum, however, had a definite, though only partial, protective

TABLE 3—*Protection Experiment* \*

Animal No	Inoculum	Symptoms	Death
1	Culture alone	Characteristic and marked in 16 hours, severe in 24 hours	30 hours
2	Culture plus normal human serum	Mild for 30 hours, then sudden development of fatal illness	36 hours
3	Culture plus normal horse serum	Characteristic, beginning within 16 hours	30 hours
4	Culture plus human encephalitis convalescent serum 499	Mild for first 20 hours then rapidly advancing, typical illness, severe, with collapse in about 27 hours	31 hours
5	Culture plus undiluted Rosenow's encephalitis antistreptococcus serum	Edema of eyes in 16 hours, otherwise no symptoms for about 40 hours thereafter increasing weakness and protracted collapse	3 days
6	Culture alone 1 hour after intravenous injection of 1.5 cc of a mixture of 0.5 cc each of three different human encephalitis convalescent serums	Characteristic, beginning within 16 hours	29 hours
7	Culture alone, 1 hour after intravenous injection of 1.0 cc of undiluted Rosenow's encephalitis antistreptococcus serum	Characteristic, marked within 16 hours	29 hours

\* Albino rabbits weighing from 1,750 to 2,200 Gm., inoculated intracerebrally with 0.1 cc of a fifteen hour old culture of strain En 29<sup>2</sup> Br R 12 A, diluted with broth 1:1,000, or with mixtures of this culture 1:500 and equal amounts of the serums listed, after the mixtures had stood at room temperature for two and one half hours.

effect, causing considerable delay in the appearance of symptoms, while the animal eventually died. In the same circumstances the human convalescent serum had no protective effect whatever (fig 1 F, G, H, I, J, K and L).

When injected intravenously an hour before the intracerebral introduction of the culture, neither the convalescent serum nor Rosenow's antistreptococcus serum offered the slightest detectable protection, on the contrary, the illness seemed, if anything, more acute.

Similar experiments were conducted with a total of seven different serums (five from convalescent human patients and two from convalescent monkeys). Four of the seven serums used had been tested and found to have marked protective power against the virus in mice. A summary of the results of all the protection experiments is given in table 4.

These results clearly indicate that Rosenow's serum had some protective power, though it was sufficient only to delay the death of the rabbits. This was to be expected, since this serum is a polyvalent anti-streptococcus serum. On the other hand, no evidence was found that any of the convalescent serums, despite their proved power to neutralize the virus of encephalitis, could protect rabbits in any degree against the effects of intracerebral inoculation with the streptococci.

TABLE 4—*Results of Protection Experiments*

Inoculum*	Number of Rabbits Inoculated	Symptoms	Average Time Before Death§
Culture alone	4	Characteristic, acute	32 hours
Mixtures of culture plus normal human serum	5	Characteristic, delayed in one case	30 hours (except one that lived 4½ days)
Mixtures of culture plus normal horse serum	4	Characteristic, acute	30 hours
Mixtures of culture plus human convalescent serum (5 different serums)†	7	Characteristic, acute	30 hours
Mixtures of culture plus monkey convalescent serum (2 different serums)‡	4	Characteristic, delayed in one case	24 hours (except one that lived 51 hours)
Mixtures of culture plus Rosenow's encephalitis antistreptococcus serum	5	Mild and delayed	3 days
Culture alone intracerebrally, 1 hour after intravenous injection of human convalescent serum	2	Characteristic and very acute in one case, some what delayed in the other	48 hours
Culture alone intracerebrally 1 hour after intravenous inoculation of Rosenow's encephalitis antistreptococcus serum	2	Characteristic, very acute	24 hours

\* Intracerebral dose in all cases was equivalent to 0.1 cc of a 1:1,000 dilution of the ten to twelve hour old dextrose brain broth cultures.

† Two of these serums had been tested and found to have marked protective power for mice against the encephalitis virus of Muckenfuss, Armstrong and McCordock.

‡ Both these serums had strong protective power against the encephalitis virus when tested in mice.

§ Death occurred within forty eight hours in all animals inoculated.

#### SUMMARY AND COMMENT

In this paper are described the results which followed intracerebral injection into animals of unpurified primary cultures from the nasopharynxes and pure cultures of streptococci originating from patients with encephalitis in St. Louis and from normal persons. For comparison with the cultures secured by us we studied the pathogenicity of strains selected by Dr. Rosenow as typical examples of the encephalitis streptococcus and we also observed rabbits inoculated personally by Dr. Rosenow. Experiments designed to investigate through agglutination reactions and protection tests the capacity of encephalitis convalescent

serums to exhibit specific immunologic reactivity toward the streptococci are reported

Of twenty-three albino rabbits inoculated intracerebrally with the primary dextrose-brain broth cultures isolated from the nasopharynxes of twenty-one different patients with encephalitis, one showed transient symptoms only, followed by complete recovery, four showed no symptoms and eighteen (78 per cent) had progressive illness and died, in most instances in about forty-eight hours after the inoculation. Similar injections of the primary cultures from the nasopharynxes of ten normal persons, six of whom resided at a considerable distance from the zone of the epidemic (Washington, D. C.) caused no symptoms in one rabbit, illness followed by partial recovery in two other rabbits and a rapidly fatal infection in the remaining seven rabbits, a mortality of 70 per cent.

Green colony streptococci were recovered from the brains of nearly all the animals dying after inoculation with primary cultures from the nasopharynx (whether these originated from patients with encephalitis or from normal persons), and frequently these streptococci were the only organisms isolated from the brain. On the other hand, these organisms were cultivated from the blood stream in a much smaller proportion of the rabbits.

Pure strains of streptococci recovered from the brains of the rabbits inoculated with the primary cultures from patients with encephalitis were reinjected into a total of thirty rabbits, and an intracerebral dose of 0.1 cc. of a 1:1,000 dilution of the young cultures was invariably fatal. There was little change in virulence observed through as many as five successive passages in animals. Strains of streptococci recovered from the brains of rabbits dying after injection of primary cultures from normal persons caused the same type of illness on reinjection into rabbits, but some of the strains were apparently somewhat less virulent than the streptococci originating from patients with encephalitis.

For comparison with the effects produced in these rabbits by injection of our own cultures, we were able to observe the reactions of a total of eighteen rabbits inoculated with streptococci isolated by Dr. Rosenow and regarded by him as representing typical encephalitis strains. Four of these animals were inoculated by Dr. Rosenow personally in our laboratory, and the remainder were inoculated by us with cultures which he sent to us. The course of the illness in these animals was practically identical with that in the rabbits inoculated with our cultures from patients with encephalitis and there seems to be no reason to doubt that we reproduced the same condition with our material as was demonstrated and described to us by Dr. Rosenow as the typical experimental encephalitis in rabbits.



In all cases the illness in the rabbits followed a fairly uniform, and to a certain degree predictable, course irrespective of the purity of the culture of streptococci injected. There was noted, however, much variation in the intensity with which particular symptoms developed in individual rabbits receiving the identical material as well as among those inoculated with cultures of different origin, and we were impressed by the ease with which a distorted impression of the whole clinical picture may be obtained if one gives special attention to changes in behavior of a particular kind or attaches special significance to a particular symptom.

Lacking the extensive experience of Dr. Rosenow which permits him to differentiate the effects produced in rabbits by injection of streptococci from patients with encephalitis from those which follow similar intracerebral injection of streptococci from patients with poliomyelitis or from other sources, we were unable to see anything definitely resembling either epidemic encephalitis or other specific human disease in the symptoms shown by these inoculated rabbits.

This conclusion is further supported by the changes noted at autopsy. The pathologic changes, like the symptoms, were of the same general character in all the rabbits examined, no matter what the source of the inoculum. The principal gross change, seen in two thirds of the seventy-two rabbits which came to autopsy, consisted in marked engorgement of the vessels of the leptomeninges. Visible meningeal exudate was present in about one third of the animals. A few more than half of the rabbits showed hemorrhagic edema of the lungs.

The sections from the brain showed on microscopic examination mainly a cellular infiltration of the meninges, with a mixture of many polymorphonuclear leukocytes and usually a smaller number of lymphocytes. The brain tissue subjacent to the meninges was often seen to be infiltrated with a similar mixture of cells. Streptococci were readily demonstrated in the meningeal exudate. Most of the sections revealed a purulent exudate in the ventricular cavities. The degree of frank meningitis apparently increased somewhat in successive passages in animals of typical encephalitis strains of streptococci. Many of the blood vessels, particularly those in the superficial cortical layers, were surrounded by cuffs consisting of polymorphonuclear cells and large lymphocytes, but only rarely could one find perivascular cuffing with round cells only. There were no significant changes in the nerve cells. No relationship could be detected between the severity of the lesions and the origin of the strain of infecting organisms. In short, the pathologic changes were mainly those of purulent meningo-encephalitis, and the lesions evidently did not correspond either in character or distribution with those characteristic of epidemic encephalitis in human patients.

Dr Rosenow, on several occasions, in personal conversation and in published papers<sup>6</sup> has expressed the view that even though a filtrable virus were demonstrated in encephalitis, this would not necessarily destroy the force of his claim for the etiologic rôle of streptococci, since he conceived it to be possible that the virus and the streptococci may be biologically related and that the cocci may represent only the visible and cultivable forms of the virus. The results of our experiments with monkeys and with convalescent serums would tend to refute such a conception.

A *Macacus rhesus* monkey inoculated intracerebrally with a heavy dose of one of Rosenow's strains (which possessed all the characteristics regarded by him as typical of encephalitis streptococci) showed mild symptoms only for a few hours after inoculation, followed by rapid and complete recovery. This illness in the monkey was of quite different character from that produced in the same species of monkey by intracerebral inoculation with the filtrable virus recovered by Muckenfuss, Armstrong and McCordock from patients with encephalitis in St. Louis. In rabbits, the same culture of this strain, greatly diluted, produced the usual acute illness, followed soon by death. On the other hand, both Muckenfuss and Webster have shown that rabbits are entirely susceptible to the St. Louis virus.<sup>7</sup>

Several specimens of the serum from patients convalescing from encephalitis failed to agglutinate any of the several strains of typical encephalitis streptococci tested and did not protect rabbits when mixed with the streptococci before intracerebral injections, while at the same time these serums did protect mice against the virus. This is further evidence that the virus and the streptococci are not related.

#### CONCLUSIONS

In reviewing the entire study it seems clear that most of the observations of Rosenow were confirmed, but the principal inferences he has drawn from them do not appear to be valid.

Specifically, we found, in agreement with the published findings of Rosenow, (1) that green colony streptococci tend to be relatively more abundant in the nasopharynges of patients acutely ill with encephalitis than in those of normal persons, (2) that the streptococci originating from the nasopharynges of patients with encephalitis often exhibit a somewhat greater degree of virulence for rabbits when tested by intra-

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6 Rosenow, E. C. *Weekly Bull. St. Louis M. Soc.* **28**: 69 (Oct. 13) 1933, *Relation of Streptococci to Filtrable Virus of Epizootic Encephalitis of Fox*. *J. Infect. Dis.* **48**: 304 (March) 1931.

7 Report on the St. Louis Outbreak of Encephalitis, *Public Health Bulletin* no. 214, Washington, D. C., Superintendent of Documents, Government Printing Office, 1935, p. 30.

cerebral inoculation than those similarly cultured from normal persons, (3) that these streptococci also possess apparently a slightly greater serologic homogeneity when tested by agglutination with Rosenow's "encephalitis antistreptococcus serum" and (4) that the medium (dextrose-brain broth) and technical procedures of Rosenow are especially well adapted to the isolation and study of the streptococci

On the other hand, we did not confirm Rosenow's findings that a certain narrow range of cataphoretic velocity is characteristic of "encephalitis streptococci." In our hands no consistent relationship between the source or virulence of the cultures of streptococci and their average velocity in the electric field was evident. Moreover, while it was true that either mixed primary cultures or pure cultures of green colony streptococci from patients with encephalitis produced in rabbits an acute illness of more or less constant character, this experimental infection could not be regarded as identical with human epidemic encephalitis, on the basis either of the symptoms or of the pathologic changes. No suggestion of a biologic relationship between the streptococci and the virus isolated from patients in St. Louis was indicated by our results. Lastly, we found no evidence that encephalitis convalescent serum had any specific reactivity toward the streptococci isolated from patients with encephalitis.

In view of the occasional isolation by Rosenow, as well as by other investigators, of green colony streptococci from specimens of the brain or spinal fluid of patients with encephalitis and the relative abundance of streptococci of this type, having a high virulence for rabbits, in the nasopharynxes of patients during the height of the disease, it does not seem justifiable to dismiss these organisms altogether from consideration. We conclude, however, that no valid evidence has been adduced which would support the view that the streptococci represent the primary etiologic agent of epidemic encephalitis in human beings or have any specific relationship to the virus isolated from patients with this disease in St. Louis. It appears that by insisting on identifying the streptococci as the primary etiologic agent Rosenow has missed the opportunity to elucidate their possible rôle as secondary invaders.

# PURPURA HAEMORRHAGICA FOLLOWING THE ADMINISTRATION OF NEOARSPHENAMINE

THE REACTION TO NEOARSPHENAMINE COMPARED WITH THE  
REACTION TO MAPIIARSEN

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Hemorrhage following the therapeutic use of the arsphenamines apparently was not reported until 1916, when Evans<sup>1</sup> mentioned the occurrence but did not connect it definitely with arsphenamine. Three years later (1919) two French observers, Labbé and Langlois,<sup>2</sup> called attention to the fact that purpuric manifestations are a complication of the arsphenamine therapy of syphilis. McCarthy and Wilson<sup>3</sup> in 1932 reviewed the published reports of eleven cases of purpura haemorrhagica following the use of arsphenamine and reported two of their own cases. Loveman<sup>4</sup> in 1932 was able to find reports of fourteen instances of purpura haemorrhagica following arsphenamine treatment up to 1931, when his article was sent to the publishers. With one new case included in his report, the total number of cases reported up to 1932, on the basis of Loveman's statistics, was seventeen (including the two cases reported by McCarthy and Wilson). Since 1932 there have been nearly as many instances reported of purpura haemorrhagica following the intravenous use of arsphenamine as during the previous

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Supported by a grant from the Christine Breon Fund

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1 Evans, F A. Observations on the Origin and Status of the So-Called "Transitional" White Blood Cell, *Arch Int Med* **17** 1 (Jan) 1916

2 Labbe, M, and Langlois, S. Purpura hemorrhagique aigue par intoxication arsénicale, *Bull et mem Soc med d hôp de Paris* **43** 786, 1919

3 McCarthy, F P, and Wilson, Robert, Jr. The Blood Dyscrasias Following the Arsphenamines, *J A M A* **99** 1557 (Nov 5) 1932

4 Loveman, A B. Toxic Granulocytopenia, Purpura Hemorrhagica and Aplastic Anemia Following the Arsphenamines, *Ann Int Med* **5** 1238 (April) 1932

eighteen years<sup>5</sup> This does not mean that the condition is relatively more frequent but probably indicates a more widespread interest and alertness in the recognition of complications due to arsphenamine, so that more instances are now being reported

It is not our purpose to attempt a comprehensive review of the literature The articles by Loveman<sup>4</sup> and McCarthy and Wilson<sup>3</sup> contain comprehensive bibliographies In a review of the recent literature on blood Sturgis and his associates<sup>6</sup> mentioned the available reported instances of purpura haemorrhagica following arsphenamine therapy occurring from 1932 to 1935

In the syphilis clinic at the University of California since 1924 about sixty thousand treatments with arsphenamine have been administered, with four recorded cases of purpura haemorrhagica The data on three of the patients, the first observed in 1931 and the other two from 1932 to 1935, constitute the material for this report

#### METHODS AND TECHNIC

Three patients were studied One was observed in the University of California Hospital during the acute phase of the condition, and was later followed in the clinic, but he soon disappeared from observation, and his subsequent history is unknown Two patients were followed in the hematologic clinic as ambulatory patients

Blood counts were made with standardized pipets, the hemoglobin was estimated by means of the Sahli method as modified by Osgood and Haskins<sup>7</sup> With this method 13.7 Gm of hemoglobin per hundred cubic centimeters of blood equals 100 per cent The Rees and Ecker<sup>8</sup> method of estimating the number of platelets was used, with from 300,000 to 400,000 platelets per cubic millimeter of blood considered as the normal range Blood counts were made between 9:00 and 10:30 a. m., usually before but at times just after treatment was given, and

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<sup>5</sup> Rich, Murray. An Unusual Hematologic Reaction to Neoarsphenamine, *J A M A* **101** 1223 (Oct 14) 1933 Bickford, J V., and Tilghman, R C. Purpura Haemorrhagica in Congenital Syphilis Following Arsphenamine, *ibid* **100** 1984 (June 24) 1933 Kostoulas, A. Hemorragies des muqueuses post-"neo 606" et sulfarsenobenzolique, *Bull Soc franç de dermat et syph* **40** 771, 1933 Chevallier, P., Colin, M., Bernard, J., and Ely, Z. Sur les formules sanguines des syndromes hemorragiques toxiques. A propos de six cas d'hemorragies post-arsenobenzoliques recueillis en un an, *Sang* **6** 917, 1932 Grund, J L. Purpura Hemorrhagica with Profuse Bleeding from the Mucous Membranes Following the Treatment of Syphilis with Bismarsen, *New England J Med* **211** 443 (Sept 6) 1934 Niles, H D. Hemorrhagic Purpura Following Bismarsen (Arsphenamin-Bismuth Preparation), *Am J Syph & Neurol* **18** 300 (July) 1934

<sup>6</sup> Sturgis, Cyrus C., Isaacs, Raphael, Goldhamer, S M., Bethell, F H., and Farrar, G E. Blood. A Review of the Recent Literature, *Arch Int Med* **55** 1001 (June) 1935

<sup>7</sup> Osgood, E E., and Haskins, H D. A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, *J Biol Chem* **57** 107, 1923

<sup>8</sup> Rees, H M., and Ecker, E E. An Improved Method for Counting Blood Platelets, *J A M A* **80** 621 (March 3) 1923

were carried out in the building in which the syphilis clinic is located. The sedimentation tests and the hematocrit readings were made with Wintrobe pipets.<sup>9</sup>

The capillary resistance tests were made with the da Silva-Mello capillary resistometer as modified by Dalldorf.<sup>10</sup> This instrument is a suction syringe attached by a rubber tube to a small glass cup, with a cuff, 8 mm in width, turned out at right angles. The syringe has attached to it a spring manometer for registering the number of centimeters of mercury of negative pressure in the cup. We applied the cup to the skin of the outer surface of the upper portion of the arm, just above the elbow, the number of petechiae produced at the end of one minute, with various levels of negative pressure, constituted the readings. After consulting with Dr. James Rinehart, of the department of pathology, who lent us the resistometer and who has made many readings in his study of subclinical scurvy, we decided to adopt the following standard. A reading of 20 cm or less, producing from six to twenty or more petechiae, indicates a decrease in the capillary resistance.

#### REPORT OF CASES

CASE 1—J. O'C., a white man aged 34, single, consulted a physician in 1931 on account of a urethral discharge, headache and general malaise. The Wassermann reaction of the blood was positive, and the patient was treated for syphilis. He received twenty-four injections each of neoarsphenamine and of a bismuth preparation. He recalled that on two occasions (dates not remembered) bleeding of the gums occurred after an injection of neoarsphenamine and that later some "purplish spots" appeared over the lower extremities. He did not mention this to his physician at the time.

No antisyphilitic treatment was administered from November 1931 to December 1932 (thirteen months). At the end of this period the patient reported to the urologic clinic of the University of California on account of a urethral discharge. As the Wassermann reaction of the blood was four plus, he was transferred to the syphilis clinic for treatment, where the diagnosis of latent syphilis was made and therapy was instituted.

The patient received twelve weekly injections of a preparation of bismuth in oil intramuscularly. On April 18, 1933, he received an intravenous injection of 0.45 Gm of neoarsphenamine. During the next two weeks he received two injections of 0.6 Gm each. One week later, on May 9, he received the fourth injection, 0.6 Gm of neoarsphenamine. Immediately after this injection the patient had a severe headache, became nauseated and vomited. One hour after the injection his gums began to bleed, and three hours later many "small purplish spots" began to appear below the knees, gradually spreading upward to the trunk and arms. Eleven hours after the injection he voided dark and smoky-appearing urine. The gums continued to bleed during the night, and in the morning a black, tarry stool was passed. The patient returned to the syphilis clinic within twenty-four hours after the injection and was transferred at once to the medical service of the University of California Hospital.

Examination showed that the skin and mucous membranes were pale and that numerous petechial hemorrhages were scattered over the body, especially on the extremities. The pupils were of unequal sizes, the right being larger than the left,

9 Wintrobe, M. M. Classification of the Anemias on the Basis of Differences in the Size and Hemoglobin Content of the Red Corpuscles, *Proc. Soc. Exper. Biol. & Med.* **27** 1071, 1930.

10 Dalldorf, Gilbert. A Sensitive Test for Subclinical Scurvy in Man, *Am. J. Dis. Child.* **46** 794 (Oct.) 1933.

and both reacted sluggishly to light. The heart and lungs appeared normal. The blood pressure was 100 systolic, and 60 diastolic. The right epididymis was enlarged and tender. The urine showed a trace of albumin, many red blood cells were present in the sediment.

The bleeding time (Duke's method) was found to be six hours. The clotting time (Lee and White) was eight minutes, and the clot did not retract after six hours. The application of a tourniquet above the elbow caused the appearance of many more petechiae below the tourniquet. The blood counts are shown in table 1.

Immediately after entry into the hospital the patient was given 15 cc of his own blood intramuscularly and then 20 units of parathyroid extract and an erythema dose of ultraviolet radiation to the back and chest. The bleeding continued. Twelve hours after admission to the hospital the patient was given a transfusion of 240 cc of whole blood from a compatible donor. Within a half-hour the bleeding stopped and did not recur.

On the following morning the bleeding time was five minutes. The patient felt perfectly well and insisted on leaving the hospital.

TABLE 1—*Data on the Blood Counts in Case 1*

Date, 1933	Hemoglobin		Red Blood Cells, Mil lions	Reticu- lo- cytes, %	White Blood Cells, Thou- sands	Polymorphonuclears, Percentage			Eosino- phils, %	Lym- pho- cytes, %	Mono- cytes, %	Plate- lets, Thou- sands
	%	Gm				Total	Fila- ment	Non fila- ment				
5/11				0.6	11.75	63	38	25	5	18	13	30
5/13	72	9.9	3.87		11.65	75	60	15	2	12	11	80
5/15						76	59	17	5	15	4	280
5/17												410
6/7				0.6		69	57	12	8	16	7	430
6/12	80	11.0	4.97		10.80	78	64	14	3	12	9	320
6/27						61	56	6	5	22	10	340

CASE 2—G. N., a white woman aged 48, married, had been under treatment for syphilis for about three months. The date of the initial infection was not known. The treatments were begun on June 24, 1933. She had had no previous treatment for syphilis, although the diagnosis was made fifteen years previously, when the Wassermann reaction of the blood was positive.

After twelve intramuscular injections of a suspension of bismuth in oil, she received an intravenous injection of 0.3 Gm of neoarsphenamine. She had chilly sensations, headache and nausea for twenty-four hours after the injection. On October 12, one week later, she was given a second intravenous injection of neoarsphenamine, of 0.15 Gm. Within a few minutes she became nauseated, and later in the evening generalized pains developed over the body, more particularly through the lumbar region and down the lower extremities. A few hours after the onset of pain "black and blue" spots appeared over the lower extremities. This was approximately eight hours after the administration of neoarsphenamine. The patient did not report to the syphilis clinic until October 19. At that time the skin and subcutaneous tissue below the knees showed dark ecchymotic areas, which were not elevated but were slightly tender. They varied in size from patches 1 to 2 mm in diameter to areas about 3 by 5 cm in extent. The bleeding time (Duke) was three minutes, and the clotting time (Lee and White) was ten minutes. The clot was firm and retractile. The ecchymotic areas and purpuric eruption had disappeared by October 25.

On November 13 the bleeding time (Duke) was three minutes, and the clotting time (Lee and White) was ten minutes with a 10 mm test tube. Between Nov 15, 1933, and May 21, 1934, she received twenty-four intramuscular injections of 0.2 Gm each of bismuth subsalicylate. Intramuscular injections of mercury salicylate were attempted but were abandoned in favor of the bismuth subsalicylate on account of pain. She also took 1 cc of potassium iodide three times daily by mouth.

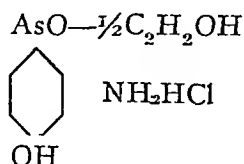
On May 29, owing to changes in the clinic staff, she was inadvertently given 0.3 Gm of neoarsphenamine. After the injection she had nausea, vomiting, chills and general malaise, and on the following morning there were a few purpuric spots on the buccal mucous membrane. On June 4 she received another dose of 0.3 Gm of neoarsphenamine, followed by an exactly similar general reaction. On the following morning (about twenty-four hours later) the skin of the extremities and trunk was covered with a purpuric eruption, with scattered areas of large ecchymotic patches, the largest about 8 by 10 cm. There were areas of ecchymosis in the buccal mucosa and over the pharynx from 2 mm to 1 cm in diameter.

The platelet count on June 6 was 10,000. The bleeding time was sixteen minutes, the clotting time, six minutes. The clot was nonretractile. Table 2 shows the results of the studies of the blood that were made.

Examination on June 6, aside from the marked purpura and ecchymosis mentioned and a palpable edge of the liver, did not show any objective signs resulting from the blood dyscrasia. The spleen was not palpable. No actual bleeding had occurred. The patient's dietary was carefully gone into at this time, but it showed no deficiency. There was no history of exposure to drugs or chemicals that might affect the hematopoietic system. It will be noted that the platelets were rapidly regenerated and that the red and white blood cells were only slightly disturbed. The bleeding time had returned to normal by June 9. Studies on capillary resistance by means of the Dalldorf apparatus<sup>10</sup> showed a lag in the return of capillary resistance to normal, according to the standard used. It will be noted that the increase of capillary resistance was slower than the rate of the platelets in returning to normal. By July 12 there were a few minute petechiae (two or three) at a pressure of 20 cm of mercury.

On October 18 we sent for this patient in order to try out carefully the effects of one of the new arsenical preparations, mapharsen<sup>11</sup>. It will be seen from table 2 that the blood was normal at this time. The first dose, 10 mg, did not produce any reaction. The table shows the immediate and the twenty-four hour variations in the platelet count. She received one injection of 10 mg, two injections of 20 mg and two injections of 30 mg, making a total of five injections, after which injections were discontinued because the hemoglobin value and the white blood cell count showed a slight fall. She had no untoward reactions from any of the injections of mapharsen and expressed the opinion that she must be improving as she felt so much better. She was then given mercury salicylate, 0.1 Gm intramuscularly each week, up to the time the blood counts were made on Jan 10, 1935.

11 Mapharsen (the hemialcoholate of meta-amino-para-hydroxyphenylarsine oxide) was supplied to us for clinical trial by Parke, Davis & Co. This preparation is obtained by the oxidation of arsphenamine and is similar to arsenoxide. It has the formula





Date	Hemoglobin		Red Blood Cells, Mil.	Platelets, Thou.	White Blood Cells, Thou.	Polymorphonuclears, Percentage				Lymphocytes, %	Monocytes, %	Notes
	%	Gm.				Total	Fila-		Fosino phils, %			
							ment	ament				
10/19/33	82	11.3	4.65	290	5.40	73	19	54	4	15	6	Cleared
10/25/33	82	11.3	4.92	290	5.60	77	16	61	2	24	7	Bleeding time, 3 minutes, clotting time, 10 minutes
11/13/33				320	6.20							Bleeding time, 16 minutes, clotting time, 6 minutes, no retraction
6/ 6/31	85	11.6	4.11	10	5.15	67	34	33	3	16	13	Hematoerit measurements Red cell volume, 36 cc Corpuscular volume, 81.6 eu microns Mean corpuscular hemoglobin, 26.3 micromg Mean corpuscular hemoglobin concentra- tion, 32.1% Volume index Saturation index, 0.947 Sedimentation rate 20 minutes, 5 mm, 40 minutes, 10 mm, normal, 2 to 4 mm in 4 hours, fragility, hemolysis began at 0.4%, com- plete at 0.25%
6/ 7/31				40								Low
6/ 8/31				50								Normal
6/ 9/31	80	11.0	4.20	100	8.65	79	47	32	2	13	5	High
6/11/34	80	11.0	4.05	160	8.55							45
6/13/34	81	11.5	4.67	180	6.10							45.0
6/15/34	77	10.4	4.08	170								80
6/16/34				180								87.0
6/19/34				181								91
6/21/34	85	11.6		230	7.00							27
6/27/34	82	11.3	4.04	300	7.60	73	17	56	2	19	6	29.5
6/29/34												32
7/10/34	75	11.6	3.62	200								33
7/20/34	73	10.0	3.90	300	7.00	75	18	37	2	15	8	35.0
7/27/34	83	11.2	3.84	270	4.65	81	48	33	3	11	5	0.904
10/18/34	90	12.3	4.00	280	6.25	61	43	18	4	24	11	1.05
				250		72	58	14	1	22	5	0.87
				220								1.23
				200								
10/19/34	80	11.0	4.02	170		65	40	25	1	20	13	Before mapharsen bleeding time, 2 minutes, clotting time 9 minutes
10/22/34				230								15 minutes after mapharsen
11/ 1/34	80	11.0	3.50	370	6.10	73	59	24		12	4	30 minutes after mapharsen
11/ 5/34				350								60 minutes after mapharsen
11/ 8/34	90	12.3	4.48	200	7.10	80	63	17	4	10	6	Sedimentation rate 15 minutes, 2 mm, 30 minutes, 7 mm, 60 minutes, 15 mm
11/13/34	77	10.5	4.80	250	4.70	76	37	39	5	9	8	Hematoerit measurements (before mapharsen) red cell volume, 35 cc, corpuscular volume, 87.5 eu microns, mean corpuscular hemoglobin, 30.7 micromg, mean corpuscular hemoglobin concentration, 35.1% volume index, 0.8, saturation index, 1.12
11/15/34	80	11.8	4.87	200	8.80	68	46	22	1	22	8	After three treatments with mapharsen
11/20/34	75	10.3	3.56	380	4.40	70	45	25	3	17	10	
11/22/34	80	11.0	4.67	270	7.75	74	46	28	3	15	6	One nucleated red cell seen in counting 100 leukocytes
11/25/34	83	11.7			8.20	75	40	35	2	15	8	
12/ 6/34	90	12.3	4.33	240	6.90	76	50	26	1	16	7	
12/13/34	85	11.7	4.20	250	5.75	71	42	29	5	17	7	
12/20/34	91	12.3	4.86	260	8.65							
1/10/35	86	11.8	5.31	210	5.00	79	53	26	4	13	1	Capillary resistance 6/11/34 6/16/34 6/27/34 7/17/34
												Pressure Of Mercury 15 17 17 17
												Retracting 10 to 12 10 to 7 10 to 7 10 to 7

The question then arose as to whether she had become in any measure desensitized to neoarsphenamine by the administration of mapharsen. The reactions to mapharsen did not suggest this, as she did not show diminishing reactions with each dose of mapharsen but showed no toxic reactions at all toward the drug. We sent for the patient again on Feb 8, 1935, to test her sensitivity to a further small dose of neoarsphenamine. The blood count, including the platelet count, appears in table 3. As soon as the 0.1 Gm of neoarsphenamine was administered she became ill, with nausea, chills and generalized pains associated with great prostration. Within one hour after the injection the platelet count dropped to 10,000 and purpuric spots began to appear on the buccal mucosa and about the ankles. There was slight bleeding from the gums. While vomiting over a stationary wash-bowl, she became dizzy and fell forward, striking the right orbital region against the wall. The trauma was slight, yet a large area of ecchymosis appeared immediately. The accompanying photograph (fig 1), taken on the day following the injection,



Fig 1 (case 2)—The purpuric and ecchymotic lesions which appeared within two hours after 0.1 Gm of neoarsphenamine was administered

shows the lesions on the arms which appeared two hours after 0.1 Gm of neoarsphenamine had been given. Recovery was rapid, as will be noted in table 3.

**CASE 3**—J. P., an Italian ex-soldier, single, aged 37, reported in November 1931 to the medical clinic of the University of California Medical School, complaining of soreness of the tongue of two weeks' duration. He had a primary penile chancre in 1927. At that time he was given three courses of intramuscular injections of a bismuth preparation and mercury. He may have received a few intravenous injections of neoarsphenamine, but he was uncertain concerning this possibility. Examination disclosed a small, shallow ulcer about 4 mm in diameter at the tip of the tongue. Aside from a rather slow pulse rate (66), a blood pressure of 100 systolic, and 70 diastolic and the lingual lesion, physical examination revealed no abnormality. The Wassermann reaction of the blood was positive. A diagnosis of recurrent secondary syphilis with mucous patches was made, and anti-syphilitic therapy was administered, consisting first of twelve intramuscular injections of bismuth subsalicylate and two intravenous injections of 0.45 Gm of

TABLE 3—Further Data on the Blood in Case 2

Date	Hemoglobin		Red Blood Cells, Mill ions	Plate lets, Thou sands	White Blood Cells, Thou sands	Polymorphonuclears, Percentage			Eosino phils, %	Lym pho cytes, %	Mono cytes, %	Comment
	%	Gm				Total	Neu- trophils	Leu- kocytes				
2/ 8/35	86	11.7	4.83	500	620							Before nearsphenamine was given 15 minutes after nearsphenamine 30 minutes after nearsphenamine 45 minutes after nearsphenamine 1 hour after nearsphenamine At the end of 1 hour petechiae appeared over forehead and in mouth, gums bled, bleeding time, 4 minutes, clotting time, 6 minutes
2/28/35	86	11.7	1.91	300	520	75	50	25	11	4	10	
				60								
				50								
				40								
				20								
3/ 1/35	75	10.2	4.56	20	855	98	21	72	3	1	3	Petechnae over upper and lower extremities and face
3/ 2/35	75	10.2		10	880	86	51	35		6	8	
3/ 4/35	80	11.0	4.45	40	800	75	44	31	4	12	9	
3/ 5/35				40								
3/ 6/35	84	11.5	4.82	100	1230	86	64	20	2	13		
3/ 8/35	80	11.0	4.54	230	780	85	70	15	2	10	3	
3/16/35				300								
3/21/35	85	11.6	4.52	300	775	77	63	8	2	8	13	
3/28/35	80	11.0	4.65	320	780	84	55	29	1	9	4	Bleeding time, 2½ minutes
4/ 4/35	90	12.3	5.27	250	1170	82	50	32	5	15	3	
4/11/35	84	11.5	5.40	260	715	88	65	23		10	2	
4/18/35	90	12.3	5.06	220	570	74	51	23	1	14	11	
5/ 7/35	87	11.9	5.57	250	745	64	49	15	1	21	14	
				220								
				230								
				200								
5/28/35	84	11.5	4.61	150	655	57	44	13	3	29	11	Before mapharsen 15 minutes after mapharsen 30 minutes after mapharsen 1 hour after mapharsen
6/10/35	90	12.3	4.77	200	1175	69	23	40	3	11	17	
6/18/35	90	12.3	4.57	170	700	71	47	24	1	19	9	
6/25/35	86	11.7	4.70	180	585	76	50	26	3	16	5	

nearsphenamine at intervals of seven days. Nausea followed each injection. The patient then went to another city to work, stopping treatment.

In March 1934, after two years, he returned and was referred to the syphilis clinic for a continuation of treatment. A course of eight weekly injections of 0.2 Gm of bismuth subsalicylate intramuscularly was administered. At weekly intervals thereafter he had three intravenous injections of 0.45 Gm of nearsphenamine. After each of the first two injections he had chilly sensations and felt feverish, faint and nauseated. After the second injection he went to bed as soon as he reached home but felt well the following morning. Immediately after the third injection, on May 29, he felt "as if he was choking," became faint and had pain in the epigastrium. He remained lying on the table in the clinic for about a half hour and then went home to bed. He was chilly and nauseated but did not vomit. In about three hours "dark spots" appeared over the lower extremities and bleeding began at the margins of the gums. He did not notice whether the urine was dark or the stool tarry. On May 31, on examination in the hematologic clinic, the skin below the knees was thickly peppered with small purpuric spots. Over both arms were scattered ecchymotic areas and some smaller purpuric spots. There was one large ecchymotic area on the upper portion of the right arm, 8 cm in extent, and a few purpuric spots were present in the buccal mucous membrane and over the hard palate. The spleen and liver were not palpable.

During the interval between May 31 and July 10, 1934, this patient received no antisyphilitic therapy or any other therapy but was followed in the hematologic clinic for study of the behavior of the blood following the episode of purpura. Physical examination showed him to be in fairly robust health. He was a particularly well developed, muscular man with no obvious infection other than syphilis. Careful inquiry was made into his dietary history, especially since 1915. From this period up to 1920, he was in the Italian army, part of the time in Serbia. His dietary was apparently adequate. There was no familial hemorrhagic tendency, and he did not know of any exposure to benzene or other poisons.

On July 10 he was again started on treatment. Between this date and October 6 he received twelve intramuscular injections of 0.2 Gm of bismuth subsalicylate. At 9:00 a.m. on October 13 0.3 Gm of nearsphenamine was administered intravenously. Nausea, general malaise and chilly sensations followed immediately. The patient went home and to bed. In about two hours the margins of the gums about the teeth began to bleed, and purpuric spots appeared in the buccal mucosa. Within three hours large ecchymotic areas appeared on the inner aspects of both arms. On October 14 he felt chilly and weak and had generalized body pains but was up and about. The next morning he reported to the hematologic clinic. Examination showed a dense shower of purpuric spots on both lower extremities. On the inner aspects of the arms were large ecchymoses, one area measuring 7 by 5 cm (fig. 2).

Following this episode he received no treatment of any kind until November 20, when he was given 10 mg of mapharsen intravenously. No toxic symptoms of any type developed. He received eight doses of mapharsen, ranging from 10 to 40 mg each. The erythrocyte, hemoglobin and platelet levels underwent no significant change while he was receiving mapharsen. He stated that he felt better than for several weeks.

On March 5, 1935, he was sent for, and with his permission 0.15 Gm of nearsphenamine was administered intravenously. As our second patient had remained so exceedingly sensitive to nearsphenamine, it became necessary to know whether this patient was still as sensitive as before the course of mapharsen. From our

knowledge of the persistent nature of neoarsphenamine sensitivity, we felt that he would still be sensitive, and that proved to be the case. Immediately after the injection he became moderately prostrated, he had chilly sensations and pain in the back and lower extremities, his face was flushed, and headache and nausea were present. Within one hour after the injection the platelet count dropped to 80,000. The capillary resistometer (Dalldorf) readings showed that the capillary resistance was beginning to decrease within the same period. Within two hours after the injection purpuric spots appeared over the tibial regions, and an ecchymotic area about 0.5 cm. in diameter appeared on the buccal mucosa. As will be noted from table 5, there was a slow return of the platelet level to normal. On the following day the patient felt recovered from his reaction except for a feeling of general malaise. He returned to work the next day, and on the fourth day after the onset of purpura several new areas appeared over the upper portion

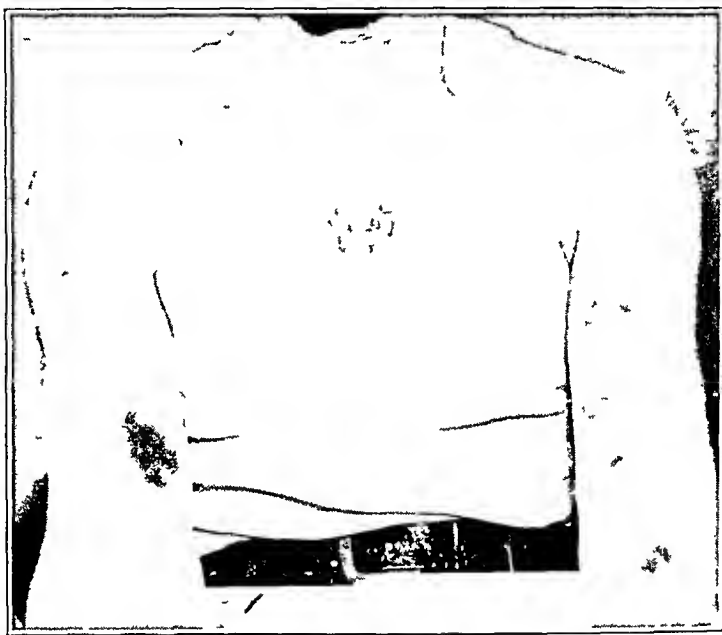


Fig 2 (case 3) —The purpuric and ecchymotic lesions which appeared within two hours after 0.1 Gm. of neoarsphenamine was administered

of the arms, apparently as the result of the strain of pushing a lawn mower for part of the day.

#### ANALYSIS OF DATA CONTAINED IN THE TABLES

Complete studies of the blood have been made in cases 2 and 3, but no attempt will be made at this time to analyze the data other than those pertaining to the platelets and the capillary resistance. The effects of neoarsphenamine and mapharsen on the formed elements of the blood are being studied in two groups of patients under treatment for syphilis. These results together with part of the data obtained in cases 2 and 3 will be discussed in a future publication.

Table 1 (case 1) shows the rapid regeneration of platelets following the toxic reaction, with bleeding and purpura haemorrhagica. This patient had an acute toxic episode with considerable oozing of blood from the mucous membrane, yet within six days after the last injection of neoarsphenamine the platelet count had returned nearly to normal.

TABLE 4—Data on the Blood in Case 3

Date	Hemoglobin		Red Blood Cells, Mil lions	Platelets, Thou sands	White Blood Cells, Thou sands	Polymorphonuclears, Percentage			Lym pho cytes, %	Mono cytes, %	Notes	Hematocrit measurements Corpuscular volume, 84 cu microns Red cell volume, 42 cc Mean corpuscular hemoglobin, 23.4 micromg Volume index, 0.93 Mean corpuscular hemoglobin concentration, 25.4%	Normal	Low	High
	%	Gm				Total	Ela ment	Nonfl ament							
5/31/34	85	11.6	5.01	60	835										
6/1/34				90											
6/2/34				100											
6/4/34				120											
6/5/34				150											
6/6/34	86	11.7	5.00	150	760	68	41	26	14	19					
6/7/34				160											
6/8/34				105											
6/9/34			4.44	220	545										
6/11/34	90	12.3	5.01	250	960	68	47	21	20	10					
6/13/34															
6/15/34	92	12.6	4.66	230	595										
6/16/34				180											
6/19/34	92	12.6	4.59	210											
6/20/34	85	11.6	4.78	270											
6/21/34				230											
6/22/34			5.07	280	405	62	56	6	2	27					
6/23/34				220											
6/26/34	83	11.3	5.15	220	830										
7/3/34	95	12.9	5.22	320	1145	69	46	23	3	15					
7/10/34	95	12.9	4.44	300	755	68	46	22	1	21					
7/17/34	96	13.1	4.97	390	1270	61	35	26	1	26					
7/21/34	80	11.0	3.55	300	905										
7/30/34	90	12.3	4.28	270	740	12	53	19	3	13					
8/7/34	81	11.5	5.22	250	795										
8/11/34	84	11.5	4.69	210	790	59	38	21	5	29					
9/29/34	92	12.6	4.42	240	660	61	37	24	1	27					
10/15/34	90	12.3	4.60	80	830	76	41	35	4	8					
10/16/34				90		73	52	21	1	18					
10/18/34				120											
10/19/34				270	1100										
10/20/34	90	12.3	4.81	230	980										
10/22/34	92	12.6	4.33	190	685										
10/27/34	86	11.7	4.33	200	1225	67	44	23	1	20					
10/30/34	83	11.3	4.46	250	865	69	37	32	6	9					
11/10/34	86	11.7	3.93	500	1320	62	36	26	2	27					
11/19/34	85	11.6	4.07	300	1305	82	39	43	1	12					
11/20/34				280	1355	88	77	11	8	3					
11/26/34	95	12.9	4.90	320	1170	66	41	25	2	16					
12/3/34	98	12.6	5.00	230	935	63	45	18	2	29					
12/10/34	95	12.9	4.20	180	960	71	47	27	1	13					
12/15/34	95	12.9	4.33	230	690	61	37	24	3	24					
12/29/34	85	11.6	4.48	250	710	66	36	30	3	26					
12/29/34	85	11.6	4.58	340	760	79	69	10	1	10					
1/5/35	95	12.9	5.19	300	1040	75	67	8		11					
1/12/35				230	985	64	42	22	1	24					
2/23/35															

Petechniae

Normal

Low

High

Hematocrit measurements

Corpuscular volume, 84 cu microns

Red cell volume, 42 cc

Mean corpuscular hemoglobin, 23.4 micromg

Volume index, 0.93

Mean corpuscular hemoglobin concentration, 25.4%

Saturation index, 0.85

Fragility starts at 0.40, complete at 0.35

Bleeding time 2½ minutes

Bleeding time, 2½ minutes, clotting time, 7½ minutes

Capillary Resistance

6/14/34

6/16/34

6/22/34

6/26/34

7/3/34

7/17/34

Many platelets on smear, 1 myelocyte

Pressure, Cm

of Mercury

10

10

15

10

15

20

10

13

20

15

20

15

20

20

25

25

25

25

25

Immediately after 0.5 cc of actin intramuscularly

One hour later

Much stuppung

One hour after first injection of morpharsen

Hematocrit measurements Red cell volume

TABLE 5—Further Data on the Blood in Case 3

Date	Hemoglobin		Red Blood Cells, Millions	Platelets, Thousands	White Blood Cells, Thousands	Polymorphonuclears, Percentage			Eosino			Lym pho cytes, %	Mono cytes, %	Comment
	%	Gm				Total	Neutrophils, %	Lymphocytes, %	Monocytes, %					
2/25/35	103	14.1	6.04	230	8.60									Before neoarsphenamine
3/ 5/35	95	13.0	4.93	280	11.40	66	44	22	2	21	11			15 minutes after neoarsphenamine
				140										1 hour after neoarsphenamine, purpura spots began to appear in mouth about 1 hour after injection of neoarsphenamine
				80										Bleeding time, 3½ minutes, clotting time, 8½ minutes, normal clot retraction
3/ 6/35				40	8.65	70	37	33	2	13	15			Before mapharsen
3/ 7/35				40	7.60	65	35	30	3	18	14			15 minutes after mapharsen
3/ 9/35	96	13.1	5.33	40	8.70	69	36	33	3	20	8			
3/11/35				80	8.60	71	45	26		24	5			
3/15/35	100	13.7		130	6.80	57	44	13		33	9			
3/18/35	96	13.1	5.31	200	6.30	65	45	20	2	22	11			
3/20/35	92	12.5	4.89	200	8.60	53	35	18	3	43	13			
3/24/35	100	13.7		240	6.75	68	45	23	4	14	14			
3/30/35	90	12.3	5.03	280	8.00	63	44	19	2	23	12			
4/15/35	84	11.5	4.12	240	6.40	63	42	21						
5/17/35	84	11.5	4.71	220	6.65	60	42	18						Before mapharsen
5/24/35	90	12.3	5.50	160	6.85									15 minutes after mapharsen
				160										1 hour after mapharsen
5/31/35	86	11.7	5.03	170	7.10	67	31	16	1	19	13			Before mapharsen
				160										15 minutes after mapharsen
				180										30 minutes after mapharsen
				180										1 hour after mapharsen
6/ 1/35	86	11.7	4.67	200	6.50	68	47	21		22	10			24 hours after mapharsen
6/11/35	86	11.7	4.38	250	7.65	53	29	24	6	28	13			

Table 2 (case 2) shows that after the first toxic episode, on Oct 12, 1933, the platelets were so rapidly regenerated that one week later (October 19), when the patient reported to the hematologic clinic, the platelet count had returned to normal. Two days after the second purpuric episode, which occurred on June 6, 1934, the platelet count was 10,000 per cubic millimeter. It required twenty-one days for the platelet level to return to normal. On Feb 28, 1935, the day on which she received 0.1 Gm of neoarsphenamine for the experimental production of purpura (table 3), the platelet count before the injection was given was 300,000 per cubic millimeter. Fifteen minutes after the injection was given the count had fallen to 60,000, within one hour to 20,000, and at the end of forty-eight hours, to 10,000. At the end of seventeen days the platelet level was again 300,000 per cubic millimeter. The results of the capillary resistance tests (Dalldorf resistometer) made on the outer aspect of the upper portion of the left arm were as follows:

Date	Pressure, Cm of Mercury	Petechiae
3/ 1/35	20	25+
	15	15+
	10	3+
3/ 6/35	20	12+
	15	10+
	10	1+
3/28/35	20	10+
	15	10+
	10	1+
4/11/35	25	3 to 6 (normal)
	20	1+ (normal)

There appears to have been a definite lag in the return of the capillary resistance as compared to the rate of return of the platelet count to normal.

After the first administration of mapharsen (10 mg) a fall of 130,000 platelets per cubic millimeter of blood occurred after twenty-four hours. The same type of immediate effect on the platelet level is noted after the initial dose of 30 mg of mapharsen at the beginning of the second course of treatments on May 7. The platelets dropped during this second course of mapharsen to levels well below what we consider normal.

Table 4 (case 3) shows that two days after the toxic reaction and the appearance of purpura haemorrhagica the platelet count was 60,000 per cubic millimeter of blood. The patient had received three doses of 0.45 Gm of neoarsphenamine before the advent of frank purpuric manifestations. The return of the platelet count to normal was slow, requiring thirty-three days. Table 4 also shows that the capillary resistance (Dalldorf resistometer) lagged behind the return of the platelets to normal. The effect of a peptone preparation on the platelet level is shown after the second attack of toxic purpura haemorrhagica. Following the injection of this preparation intramuscularly the platelet count rose from 120,000 to 250,000 in one hour, but twenty-four hours later it had dropped to 190,000, suggesting that the initial rise was a redistribution phenomenon. The return of the platelet count to normal after the second toxic episode was more rapid, requiring only fifteen days. The injection of the peptone preparation might have been a factor in bringing about this shorter period, as compared with the first period of thirty-three days.

Table 5 (case 3) shows that after the injection of 0.15 Gm of neoarsphenamine, on March 5, 1935, for the experimental production of purpura, the platelet count fell to 40,000 at the end of twenty-four hours and gradually rose until March 30, when it had reached 280,000. During the second course of treatment with



mapharsen the count again fell below normal levels. The estimations of capillary resistance (Dalldorf resistometer) in the upper portion of the left arm were as follows

Date	Pressure, Cm of Mercury	Petechiae
3/5/35	25	10+
	20	20+
	15	10+

These readings were taken one hour after 0.15 Gm of neoarsphenamine had been injected. It was obvious that the resistance was decreasing while the tests were in progress.

Date	Pressure, Cm of Mercury	Petechiae
3/7/35	20	18+
	15	10+
3/9/35	25	15+
	20	10+
	15	7+

It was about fifteen days before the readings were within the normal range. In this instance the return of the capillary tone was more rapid than the return of the platelets, which showed a marked lag.

#### SENSITIVITY TO ARSENIC

The suggestion naturally presents itself in connection with the absence of a toxic reaction after the administration of mapharsen that the quantity of arsenic is the important factor. Mapharsen contains less arsenic according to atomic weight than neoarsphenamine. About 19 per cent of neoarsphenamine is arsenic, while mapharsen contains 29 per cent. One tenth gram of neoarsphenamine, which was the amount used in our last sensitivity tests, contains about 19 mg of arsenic. Forty milligrams of mapharsen, which was the largest dose administered to our two patients, contains 12 mg of arsenic. It does not seem probable that the quantitative difference between 19 and 12 mg of arsenic would account for a sharp toxic reaction with one dose and no reaction with the other. However, the reaction to arsenic, as exhibited by various patients, must have a quantitative factor. The question arises as to whether there is not some product formed by the oxidation of arsphenamine in the body that is responsible for the toxic reactions. In order to investigate this question further, we tested the second and third patients to different combinations of arsenic, complete blood counts being made before and after each test.

Arsenic	Case 2	Case 3
Solution of potassium arsenite, 1 cc daily for 1 week	No change in blood count, no change in platelet level	No change in blood count, no change in platelet level
2 cc of sodium cacodylate, 19% strength	Before intravenous injections, 160,000 platelets, one half hour after injections, 160,000 platelets, no change in blood count	Before injection, 210,000 platelets one half hour after injection, 220,000 platelets, no change in blood count
Tryparsamide, 2 Gm intravenously	Before injection, 180,000 platelets, 15 minutes after injection 200,000 platelets 1 hour after injection, 170,000 platelets no noteworthy change in blood count	Before injection, 200,000 platelets 15 minutes after injection 230,000 platelets 1 hour after injection 220,000 platelets monocytes rose from 13% before to 25% 1 hour after injection

Some persons are so sensitive to solution of potassium arsenite that 1 or 2 drops well diluted in water will cause nausea and gastro-intestinal irritation. In our cases 2 and 3 no untoward effects were noted. Intravenous injections of both sodium cacodylate and tryparsamide likewise did not cause untoward symptoms, and no hemorrhagic or purpuric manifestations occurred. The platelet counts of both patients were below normal when these tests were carried out (between July 6 and Aug 6, 1935), but it should be recalled that three episodes of toxic purpura following the injection of neoarsphenamine and two courses each of mapharsen preceded these tests.

From the data obtained, we believe that these two patients were not sensitive to inorganic arsenic and that they were not sensitive to arsenic in combination with benzene, as evidenced by the absence of reaction to 2 Gm of tryparsamide. They were obviously sensitive to the combination of arsenic in the neoarsphenamine radicle.

#### COMMENT

These three patients showed two distinct types of sensitivity to neoarsphenamine. The first patient became increasingly sensitive until a crisis occurred in the form of a severe reaction followed by purpura haemorrhagica. He was sensitive in 1931 during the first course of neoarsphenamine treatment, for he recalled at least two occasions when he had mild hemorrhagic manifestations. Apparently no nitritoid reaction preceded the bleeding. The fact that he received no arsenicals and no treatment of any kind for a year did not suffice to abolish the sensitivity, as evidenced by the severe reaction after the fourth dose of neoarsphenamine in the second series of treatments. This patient's response to neoarsphenamine stresses the importance of a careful inquiry concerning previous reactions before arsenphenamine or its derivatives is administered.

The other two patients belong to a group, probably small, that present an initial sensitivity to neoarsphenamine. The second patient presented marked hypersensitivity to the drug from the standpoint of a toxic reaction of the platelets and capillaries. McCarthy and Wilson<sup>3</sup> in their reports collected from the literature cited one case in the thrombocytopenic group in which the complication occurred a few days after the fifth dose of neoarsphenamine. This case was reported by Jensen.<sup>12</sup> Such cases illustrate that sensitivity is not dependent on the amount of the drug previously administered. Our second patient had not received any arsenphenamine previous to Sept 28, 1933, when she received her

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<sup>12</sup> Jensen, Julius. Purpura Hemorrhagica Following Neoarsphenamin, Minnesota Med **12** 689 (Nov.) 1929.

first dose of neoarsphenamine. After the second dose of 0.15 Gm purpuric manifestations appeared. She had a nitritoid reaction after each dose. It is important to recall that when she reported to the hematologic clinic one week after receiving the second dose, although the purpuric spots were still well marked, the platelets had returned to a normal number and the bleeding time was normal. Were it not for subsequent observations, we probably would have considered the hemorrhagic manifestations as purpura simplex. The marked sensitivity to neoarsphenamine presents a sharp contrast to the entire lack of any untoward reaction from mapharsen. This applies to both the second and the third patient and certainly suggests that the sensitivity is not to arsenic as such but to some oxidation product not present in mapharsen. This is of considerable importance, as Cole and his co-workers<sup>13</sup> after a study of one thousand, two hundred and twelve patients treated with arsphenamine or its derivatives stated

In a number of instances the patient was sensitive to more than one type of arsphenamine so that, even after a premonitory symptom caused a change in the type of arsphenamine used, the patient experienced a second and in some instances a third reaction, or even more, in fact, there were 338 actual complications found among the 214 persons. If the patient is susceptible to one arsenical, the chances of using another are lessened, and this sensitivity persists.

This refers to all complications and reactions and not specifically to purpura haemorrhagica, but the latter is a complication of such severe toxicity that one would naturally hesitate to use any further arsphenamine. The question as to whether mapharsen can be safely used after the occurrence of purpura haemorrhagica is answered in the affirmative by the results in our two cases but requires further observation.

#### SUMMARY AND CONCLUSIONS

Three cases are reported in which severe toxic constitutional reactions accompanied with purpura haemorrhagica followed the administration of neoarsphenamine. One of the patients showed sensitivity after several injections of neoarsphenamine, the other two presented an initial sensitivity to the drug.

Evidence is offered suggesting that the actual amount of arsenic entering the circulation is not the important factor in determining the toxic reaction, although it may be one factor, the important factor is probably some oxidation product formed by the breaking down of neoarsphenamine in the body.

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13 Cole, H. N., DeWolf, Henry, McCuskey, J. M., Miskjian, H. G., Williamson, G. S., Rauschkolb, J. R., Ruch, R. O., and Clark, Taliaferro. Toxic Effects Following Use of the Arsphenamines, *J. A. M. A.* 97: 897 (Sept. 26) 1931.

No toxic reaction, no purpura haemorrhagica and no significant fall of the platelet count occurred after the administration of mapharsen.

Our studies suggest a distinct relationship between nitritoid crises following the administration of arsphenamine and its derivatives and the development of thrombocytopenic purpura haemorrhagica. This relationship stresses the importance of making blood counts for all patients who show nitritoid reactions after the administration of the arsphenamines.

We have demonstrated the fact that the capillary lesion is as important as the thrombopenia as a factor in the production of the purpuric manifestations.

# INFECTIOUS MONONUCLEOSIS

## FURTHER STUDIES

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The interest in infectious mononucleosis stimulated by the work of Paul and Bunnell<sup>1</sup> continues to increase, as is shown by the number of publications on the subject that have appeared since these investigators established a serologic test for diagnosing the condition

In a previous report<sup>2</sup> the clinical and cytologic aspects of the disease were reviewed. Serologic analyses of the serums of thirteen patients were given, and the nature of the sheep cell antibodies in the blood of these patients was discussed. A modification of the test originally devised by Paul and Bunnell was introduced as an aid in the diagnosis of borderline cases. This modification has eliminated or confirmed suspicious clinical observations in many cases but has failed to do so in others. The serologic diagnosis of infectious mononucleosis in the early stages of the disease or when there is mild involvement is frequently hampered by the presence of normal sheep heterophile antibodies in the blood of the patient. Our principal purpose in the present communication is to show that it is now possible to detect the presence of sheep heterophile antibodies due to infectious mononucleosis even in serum containing normal heterophile antibodies in excess. Using the technic to be described, a diagnosis of the disease can be made before the original test of Paul and Bunnell or our modification shows definitely positive results. Serum sickness in which there is also an increase in the sheep heterophile antibodies<sup>3</sup> can be distinguished from infectious

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1 Paul, J R, and Bunnell, W W. *Am J M Sc* **183** 90, 1932

2 Stuart, C A, Burgess, A M, Lawson, H A, and Wellman, H E. Some Cytologic and Serologic Aspects of Infectious Mononucleosis, *Arch Int Med* **54** 199 (Aug) 1934

3 (a) Davidsohn, I. *J Immunol* **18** 31, 1930 (b) Stuart, C A, Tallman, Juanita, and Brintzenhoff, Esther. *ibid* **28** 85, 1935

mononucleosis, and, furthermore, a correct diagnosis can be made when a patient is suffering from both diseases

In table 1 are shown the titers of the serums of twenty patients with infectious mononucleosis who have not previously been reported on. For the most part, from two to five tests were made for each patient at intervals during the course of the disease. In each case, however, only the highest titer is recorded in the table. Agglutinating titers for sheep cells in the different cases ranged from 1/160 to 1/10,240, and lytic titers ranged from 1/320 to 1/10,240.

TABLE 1—*Titers for Sheep Cell Antibodies in the Serum of Persons with Infectious Mononucleosis\**

Case Number	Agglutinins													Lysins												
	5	10	20	40	80	160	320	640	1,280	2,560	5,120	10,240	20,480	5	10	20	40	80	160	320	640	1,280	2,560	5,120	10,240	20,480
29	4	4	4	4	4	4	4	4	4	3	2	1	0	4	4	4	4	4	4	4	4	4	3	1	0	
30	4	4	4	4	4	4	4	4	4	3	1	0	0	4	4	4	4	4	4	4	4	4	3	1	0	
31	4	4	4	4	4	4	4	4	4	3	1	0	0	4	4	4	4	4	4	4	4	3	2	0	0	
32	4	4	4	4	3	1	0	0	0	0	0	0	0	4	4	4	4	3	1	0	0	0	0	0	0	
33	4	4	4	4	4	4	4	4	4	3	1	0	0	4	4	1	4	4	4	4	4	3	2	0	0	
34	4	4	4	4	4	4	4	3	2	0	0	0	0	4	4	4	4	4	4	3	1	0	0	0	0	
35	4	4	4	4	4	4	2	0	0	0	0	0	0	4	4	4	4	4	4	2	0	0	0	0	0	
36	4	4	4	4	4	4	4	4	4	3	2	0	0	4	4	4	4	4	4	4	4	3	1	0	0	
37	4	4	4	4	4	4	4	4	3	2	0	0	0	4	4	4	4	4	4	4	4	3	1	0	0	
38	4	4	4	4	3	2	1	0	0	0	0	0	0	4	4	4	4	4	3	1	0	0	0	0	0	
39	4	4	4	4	4	4	4	4	2	1	0	0	0	4	4	4	4	4	4	4	4	2	0	0	0	
40	4	4	4	4	4	4	3	2	1	0	0	0	0	4	4	4	4	4	4	3	1	0	0	0	0	
41	4	4	4	4	4	4	4	4	2	1	0	0	0	4	4	4	4	4	4	4	3	2	1	0	0	
42	4	4	4	4	4	4	3	2	1	0	0	0	0	4	4	4	4	4	4	3	1	0	0	0	0	
43	4	4	4	4	4	4	4	3	1	0	0	0	0	4	4	4	4	4	4	4	2	1	0	0	0	
44	4	4	4	4	4	3	2	0	0	0	0	0	0	4	4	4	4	4	3	1	0	0	0	0	0	
45	4	4	4	4	4	4	4	4	3	1	0	0	0	4	4	4	4	4	4	4	3	2	0	0	0	
23 46	4	4	4	4	3	1	0	0	0	0	0	0	0	4	4	4	4	4	2	0	0	0	0	0	0	
29 47	4	4	4	4	4	4	3	2	0	0	0	0	0	4	4	4	4	4	3	2	0	0	0	0	0	
48	4	4	4	4	3	1	0	0	0	0	0	0	0	4	4	4	3	2	0	0	0	0	0	0	0	

\* 4 signifies a complete reaction, 3, 2 and 1 signify a partial reaction, and 0, signifies no reaction.

It will be noted that in every case the titers of the two antibodies are practically parallel. This is somewhat unusual, as pointed out by Meyer,<sup>4</sup> since the injection of heterophile antigen into appropriate laboratory animals produces high lytic titers with little or no agglutinating antibodies for sheep cells. Ash,<sup>5</sup> working in these laboratories, obtained lytic titers of 1/80,000 for sheep cells, while the agglutinating titer of the same serums was only 1/40 or 1/80 after the prolonged immunization of rabbits with heterophile antigens. This seems to indicate either

4 Meyer, K. *Med Klin* 29:981, 1933.

5 Ash, R. Personal communication to the authors.

that the antigen concerned in the production of sheep cell antibodies in infectious mononucleosis is different from those commonly encountered or that the reaction of man to heterophile antigens in general is different from that of most animals. This seems not impossible, as the injection of horse serum which contains heterophile antigen into man frequently produces a marked increase both in sheep cell agglutinins and in lysins, the increases in the titers of the two antibodies often being parallel. As Bailey and Raffel<sup>6</sup> pointed out, one ordinarily anticipates a much higher lytic than agglutinating titer for heterologous erythrocytes in normal or immune blood of man or of animals, yet we have found that the agglutinins for rabbit cells in normal human serum greatly exceed the lysins for these cells. It will be shown in a subsequent paper that the injection of type A human cells into a rabbit may on occasion produce a high agglutinating titer for these cells without materially increasing the lytic titer. Such considerations, while lacking practical application at the present time, are of great theoretical interest, as they relate to the controversial unitarian hypothesis of antibodies.

In the course of infectious mononucleosis there is usually a sharp rise in the number of heterophile antibodies in the blood, followed in several days by a gradual lowering of the titer. In a few cases the titer completely disappeared about two weeks after the first appearance of the antibodies. Case 29, on the other hand, represents the opposite extreme. The first specimen of blood taken during the acute stage of the disease showed an agglutinating titer of 1:10,240, and this titer persisted for over one month. At the end of approximately two and one-half months the last specimen taken still gave a titer of 1:320. Fifteen of our patients were tested from six months to one year after recovery from the disease, but in no case were antibodies of the infectious mononucleosis type present.

It should be pointed out here that in our investigation both agglutinins and lysins were studied. For diagnostic purposes, however, it is more satisfactory to work with agglutinins in this disease, because variation from the average normal titer appears to be far less with this type of antibody.

In order to obtain more information regarding the nature of the sheep cell agglutinins in infectious mononucleosis, serums giving a positive reaction were adsorbed with raw and boiled cells and with emulsions of kidney (beef, rabbit, guinea-pig, swine, cat and chicken). In these experiments 0.5 cc of the cells or 0.15 cc of the tissue emulsion was added to 2 cc of a 1:2.5 or a 1:5 dilution of the serum. The tubes were then kept at room temperature for one hour. After centrifugation the supernatant fluid was removed, a portion was tested for sheep cell

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6 Bailey, G. Howard, and Raffel, Sidney. *J. Clin. Investigation* **14**: 228, 1935.

agglutinins and the remainder was reabsorbed. This procedure was repeated until three adsorptions with the various antigens were completed.

These adsorption tests showed that of all the cells and tissues used only beef cells removed the increased agglutinins from the serum of patients with infectious mononucleosis. It has already been shown<sup>7</sup> that the failure of sheep cells to agglutinate in such serums after successive adsorption with highly turbid emulsions of guinea-pig kidney, as reported in a previous paper,<sup>2</sup> was not due to the specific adsorption of the heterophile antibodies.

The fact that beef cells, either raw or boiled, remove the sheep heterophile agglutinins from the serum of persons with infectious mononucleosis is important, since it will be shown later in this paper that these cells do not remove the sheep heterophile agglutinins from normal serum. If after the adsorption of a serum with beef cells the titer for

TABLE 2—*Adsorption of Selected Normal Serum and Serums of Persons with Infectious Mononucleosis and with Serum Sickness*

Serum Adsorbed with Beef Cells and Guinea Pig Kidney	Normal Serum*								Serum of Persons with Infectious Mononucleosis								Serum of Persons with Serum Sickness							
	15	10	20	40	80	160	320	640	15	10	20	40	80	160	320	640	15	10	20	40	80	160	320	640
Before adsorption	4	4	4	4	4	4	2	0	4	4	4	4	4	3	1	0	4	4	4	4	4	3	1	0
After adsorption with beef cells	4	4	4	4	4	4	2	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
After adsorption with guinea pig kidney	0	0	0	0	0	0	0	0	4	4	4	4	4	3	1	0	0	0	0	0	0	0	0	0

\* This serum was tested both before and after adsorption with a 0.05 per cent suspension of sheep cells rather than with the usual 0.5 per cent suspension, which accounts for the exceptionally high normal titer.

sheep cells is completely or materially reduced, the serum is not normal. Bailey and Raffel<sup>6</sup> have reported similar findings. Unfortunately, a final diagnosis of infectious mononucleosis after adsorption with beef cells only is open to two objections. In the early stages of the disease, if the normal heterophile agglutinins are in excess of those due to infectious mononucleosis it will be impossible to make a correct diagnosis. Furthermore, if horse serum has been injected into the patient, there will usually be a marked increase in the sheep heterophile agglutinins, which will also be adsorbed by beef cells.

Table 2 shows the results of the adsorption with beef cells and guinea-pig kidney of a selected normal serum with a high titer and of the serum of a person with infectious mononucleosis and of the serum of a person with serum sickness adjusted to the same sheep cell titer as the normal serum. It will be noted that the sheep cell antibody from



normal serum is not removed by beef cells but is completely removed by guinea-pig kidney. On the other hand, the reverse is true of the serum of a person with infectious mononucleosis, beef cells adsorb the antibody, and guinea-pig kidney does not. The increased sheep cell antibody in the serum of a person with serum sickness is adsorbed by both beef cells and guinea-pig kidney. Therefore, the adsorption of a serum with both the cell and the tissue specified eliminates all possibility of confusing the serum of a person with infectious mononucleosis with either a normal serum of high titer or the serum of a person with serum sickness.

It seems from this that the sheep heterophile agglutinins in the three types of serum are all different. This aspect of the question, together with the relation of these antibodies to the heterophile antigen in human cells of types A and AB, has been discussed in a previous paper <sup>7a</sup>

Since it can easily be ascertained whether in an apparent case of infectious mononucleosis horse serum has recently been injected, it might appear that a test differentiating between these two diseases is superfluous. Davidsohn,<sup>8</sup> however, reported an increase in the sheep cell antibodies in the blood of patients from one to three years after treatment with horse serum. The following cases further emphasize the necessity of such a test.

#### REPORT OF CASES

**CASE 23-46**—The patient was admitted to the Charles V Chapin Hospital on Feb 17, 1935, with a condition suggestive of meningitis. Therapeutic serum was administered, and later the meningococcus was isolated from both the nasopharyngeal secretion and the spinal fluid. Serum sickness developed, and the serum was tested and adsorbed according to our routine procedure. Table 3 (February 27) clearly shows that the sheep cell antibodies were of the type present in serum sickness. Two weeks later more serum was obtained. In experiments not connected with this investigation the serum reacted peculiarly. It was then adsorbed with beef cells and guinea-pig kidney, with the results shown in table 3 (March 14). The complete removal of the sheep cell agglutinins by beef cells and the failure of guinea-pig kidney to adsorb this antibody completely after three successive adsorptions made it apparent that antibodies of the type found in infectious mononucleosis as well as those of the type found in serum sickness were present in the serum.

**CASE 29-47**—D A, a 7 year old boy, was admitted to the hospital on April 14, 1935, with signs and symptoms suggestive of meningitis. The spinal fluid showed intracellular gram-negative diplococci, which were later grown in culture. The diagnosis was meningococcic meningitis.

Lumbar puncture was performed every day from April 14 to 20, inclusive. Serum obtained from the Massachusetts Board of Health was administered as follows: 1 vial intraspinally, 2 vials intracisternally, 2 vials intramuscularly and

<sup>7a</sup> Stuart, C A, Fulton, MacDonald, Ash, Roy P, and Gregory, K K  
*J Infect Dis* **59** 65, 1936

<sup>8</sup> Davidsohn, I *J Immunol* **16** 259, 1929

2 vials intravenously on April 14, 3 vials intraspinally on April 15, and 1 vial by each route on April 16 to 19, inclusive

The temperature was irregular but elevated until April 20, when it reached 99 F. The maximum temperature was 105 F on April 15. The curve of the pulse rate corresponded with that of the temperature. The temperature remained at 99 F or lower until April 25, when it rose and was irregularly maintained until May 2. Urticaria was noted, and a diagnosis of serum sickness was made. The maximum rise in temperature in this episode was to 103 F. On May 3 the temperature rose to 103.8 F, and it remained irregularly elevated until May 8, when it reached 106.4 F by rectum. On May 3 enlargement of the cervical lymph nodes was noted both anteriorly and posteriorly. The axillary nodes, especially in the left axilla, and the inguinal nodes were enlarged. At this time "real tonsillitis" with exudate was noted and treated by irrigations with solution of sodium

TABLE 3—*Absorption of Serums from Patients in Cases 23-46 and 29-47*

Case	Date		5	10	20	40	80	160	320	640	1,280	2,560	5,120	10,240
23 46	2/27/35	Before adsorption	4	4	4	4	4	4	4	3	2	0	0	0
		After adsorption with beef cells	2	0	0	0	0	0	0	0	0	0	0	0
		After adsorption with guinea pig kidney	0	0	0	0	0	0	0	0	0	0	0	0
	3/14/35	Before adsorption	4	4	4	4	4	4	4	4	3	1	0	0
		After adsorption with beef cells	2	0	0	0	0	0	0	0	0	0	0	0
		After adsorption with guinea pig kidney												
		First adsorption	4	4	4	4	3	1	0	0	0	0	0	0
		Second adsorption	4	4	4	4	2	0	0	0	0	0	0	0
		Third adsorption	4	4	4	4	2	0	0	0	0	0	0	0
	4/21/35	Before adsorption	4	4	4	4	4	4	3	1	0	0	0	0
		After adsorption with beef cells	0	0	0	0	0	0	0	0	0	0	0	0
		After adsorption with guinea pig kidney	0	0	0	0	0	0	0	0	0	0	0	0
	5/9/35	Before adsorption	4	4	4	4	4	4	4	4	3	2	0	0
		After adsorption with beef cells	0	0	0	0	0	0	0	0	0	0	0	0
		After adsorption with guinea pig kidney												
		First adsorption	4	4	4	4	4	3	2	0	0	0	0	0
		Second adsorption	4	4	4	4	4	3	1	0	0	0	0	0
		Third adsorption	4	4	4	4	4	3	1	0	0	0	0	0

chloride. A diagnosis of infectious mononucleosis was suggested, and the record stated that enlargement of the glands had persisted longer than is usual in serum sickness.

On May 8 the temperature was 106.4 F by rectum, the pulse rate, 164, and the respiratory rate, 40. The patient was pale and alert and did not appear to be in a toxic condition. The ears were normal. The throat was slightly infected, and the tonsils were enlarged. The neck was not stiff. The glands were not so greatly enlarged but were noticeable in the neck, axillae, epitrochlear region and groins. Percussion revealed that the heart was slightly enlarged. There was a moderately loud, blowing systolic murmur.

On May 8 blood culture showed growth of a weakly hemolytic streptococcus.

Microscopic examination of the blood on May 8 revealed 20,000 leukocytes, 78 per cent polymorphonuclears, 14 per cent small lymphocytes, 1 per cent large lymphocytes, 7 per cent endotheliocytes (or monocytes) and 1 per cent eosinophils.

*Comment*—In this case, as in case 23-46, the diagnosis was meningococcic meningitis. Horse serum was injected and serum sickness developed. The serum was tested and adsorbed in the usual manner. The sheep cell agglutinins, according to the tests reported here and to others, were clearly typical of serum sickness. During the convalescence of this patient, symptoms comparable to those present in infectious mononucleosis were evident. The serum was adsorbed with beef cells and guinea-pig kidney. Table 3 shows that a result identical with that in case 23-46 was obtained. Antibodies of the type found in serum sickness were present, nevertheless, antibodies of the type found in infectious mononucleosis could be demonstrated.

CASE 43—A third case (table 1) involving meningococcic meningitis but different from the two cases just discussed is of interest. A few hours after the patient's admission to the hospital meningococci were observed in the spinal fluid. A test of the serum was positive for infectious mononucleosis. The patient died twenty-four hours later. The strain of *Meningococcus* isolated from the spinal fluid failed to adsorb any sheep heterophile antibodies from the serum.

It is possible, of course, that the connection between meningococcic meningitis and infectious mononucleosis in the cases reviewed was merely coincidental. Five other patients with meningococcic meningitis showed no symptoms of infectious mononucleosis, nor could sheep cell antibodies typical of infectious mononucleosis be demonstrated at any time during the course of the disease. Bunnell<sup>9</sup> observed no increase in sheep cell agglutinins in several cases of the disease. Yet until more is known about the etiology of infectious mononucleosis, such observations should not be overlooked. The importance of these observations lies not so much in the causal relation of the meningococcus to infectious mononucleosis as in the association of the organism in infections of the upper respiratory tract to infectious mononucleosis. There is some question in the minds of many physicians who have encountered infectious mononucleosis as to whether it is a disease entity or merely an unusual reaction to an infection of the upper respiratory tract caused by any of a number of organisms.

The uncertainty as to the status of the disease as an entity is heightened by the fact that cases occur in which the clinical picture is doubtful. A mild infection of the upper respiratory tract or an infection of the throat, associated with slight tenderness and moderate or marked enlargement of the cervical lymph nodes and a blood picture in which the percentage of lymphocytes is higher than usual and in which the characteristic so-called abnormal immature lymphocytes are seen in moderate number, presents a picture which may well be considered typical of a borderline condition. In cases of such a condition

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<sup>9</sup> Bunnell, W. W. *Am J M Sc* 186 346, 1933

the serologic test has been a definite means of differentiation. In our experience, in these cases of the borderline type serologic tests for the characteristic agglutinins have almost invariably proved negative. This, coupled with the fact that the typical form of the disease is definite clinically and cytologically and a high titer for agglutinins of the type described is usually shown, has given us the impression that we are dealing with a definite entity.

However, the demonstration of agglutinins of the type found in infectious mononucleosis in the blood of patients with meningococcic meningitis, as described in this paper, is of unusual interest as a possible illustration of the occurrence of these antibodies in patients who do not show the clinical picture of infectious mononucleosis. In one of these cases (case 43) the patient died within twenty-four hours of his admission to the hospital, and no cytologic studies were made, so the presence of coincidental infectious mononucleosis must be considered as possible. In case 23-46 the serum of the patient was sent to us as a matter of routine, and cytologic studies were made. This patient, however, did not at any time present the clinical or cytologic picture of infectious mononucleosis. The case of the other patient (case 29-47), however, is of special interest in that definite clinical and cytologic data are available. A 7 year old boy, after definite serum sickness, had what the records stated was "real tonsillitis" and enlargement of the lymph nodes suggestive of infectious mononucleosis. Five days later, at a time when the cytologic manifestations of this disease would ordinarily have been at their height, the blood count showed, on the contrary, a total of 20,000 leukocytes per cubic millimeter and the following differential count (May 8, 1935): 78 per cent polymorphonuclears, 14 per cent small lymphocytes, 1 per cent large lymphocytes, 7 per cent endotheliocytes and 1 per cent eosinophils. The picture was further complicated by the fact that on the day that this specimen of blood was taken the patient showed a rise in temperature to 106.4 F and weakly hemolytic streptococci were observed in the blood culture. Here, then, is an instance of the appearance in a patient suffering from serum sickness following treatment for meningococcic infection of a clinical picture resembling infectious mononucleosis and the coincident appearance of the agglutinins typical of the disease, without the characteristic cytologic changes.

A number of widely different bacteria have been proposed as the cause of infectious mononucleosis. Members of the streptococcus group,<sup>1</sup> diphtheroid bacilli<sup>10</sup> and Vincent's organisms<sup>11</sup> are terms perhaps most

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10 Murray, E. G. D., Webb, R. A., and Swann, M. B. R. *J. Path. & Bact.* **29**: 407, 1926.

11 Nyfeldt, A. *Compt. rend. Soc. de biol.* **101**: 590, 1929.

frequently associated with this disease. The close association of Vincent's angina and infectious mononucleosis has led some authors to state the belief that this association is not a mere coincidence (Gorham, Smith and Hunt<sup>12</sup>). The uniform failure of the organisms associated with this disease to produce heterophile antibodies in the rabbit does not rule out such organisms as the causative factor, since the heterophile antibodies in this disease are not at all comparable to those produced in rabbits by ordinary heterophile antigens.

In one of our cases (case 41) one of us (Welch) isolated a diphtheroid organism which grew sparsely on several different types of enriched medium. When freshly isolated, this organism agglutinated strongly in the serum of this patient and in the serums of four other patients known to have infectious mononucleosis. Furthermore, the organism removed small but significant amounts of sheep cell antibodies from these serums. After several transplants had been made, however, the organism completely lost its agglutinating and adsorptive properties. Heterophile antibodies were not demonstrated in rabbits into which this organism had been injected, nor did large doses of the living organism affect rabbits adversely. Through the courtesy of Caspar G. Burn it was possible to compare this organism with two strains of *Listerella monocytogenes* (Murray and his associates<sup>10</sup>) and with two strains similar to Murray's organism isolated by Burn<sup>13</sup> from the blood of patients with meningo-encephalitis. No significant morphologic, biochemical or serologic relationship has as yet been demonstrated between the four strains obtained from Burn and the organism isolated in our case 41.

#### COMMENT

The value of the serologic test devised by Paul and Bunnell in the diagnosis of infectious mononucleosis has been clearly demonstrated in several recent papers. The test as ordinarily applied, however, is not wholly specific, since normal serum of high titer may occasionally be reported as giving a positive reaction. Furthermore, persons into whom horse serum has been injected frequently show high titers for sheep cell agglutinins which by routine agglutination tests cannot be distinguished from those of patients with infectious mononucleosis. The adsorption of the serum of a patient suspected of having infectious mononucleosis with both beef cells and emulsions of guinea-pig kidney permits a complete analysis of the type or types of sheep heterophile antibodies present. Only the complete removal of these antibodies by guinea-pig kidney indicates a normal serum, the adsorption of all or most of the antibodies by beef cells and their complete adsorption by guinea-pig

12 Gorham, L. W., Smith, D. T., and Hunt, H. D. *J. Clin. Investigation* 7: 504, 1929.

13 Burn, C. G. *Proc. Soc. Exper. Biol. & Med.* 31: 1095, 1934.

kidney indicates a serum of the type present in serum sickness. In the majority of cases a diagnosis of infectious mononucleosis can be made clinically and serologically without the aid of adsorption tests, but their use in doubtful cases in which there is a low titer or in which complications of serum sickness are present makes possible a sure diagnosis.

These findings clarify the diagnosis of infectious mononucleosis but contribute little to the question of the actual origin of the antibodies under consideration. It is conceivable that the antibodies are of intrinsic origin, that they are, in a sense, auto-antibodies produced in response to the release into the blood plasma of a protein normally confined to the body cells. If this were true it would not be so difficult to explain the presence of the increases in sheep cell antibodies in diseases other than infectious mononucleosis such as have been reported in this paper and by Paul and Bunnell,<sup>1</sup> Ramsdell and Davidsohn,<sup>14</sup> Bernstein,<sup>15</sup> Boveri,<sup>16</sup> Deicher<sup>17</sup> and others.

It is not possible at the present time to determine with certainty whether infectious mononucleosis has appeared in epidemic form. Reports of epidemics previous to the establishment of the serologic test appear in some cases to be definite. Epidemics apparently of this disease have usually occurred among children, in whom symptoms were especially mild. A review of the forty-eight cases that we have encountered shows that for the most part these were clearly sporadic. Exceptions have occurred, however. One patient (case 39), a physician, had infectious mononucleosis clinically on Feb 23, 1935. This was confirmed by a blood smear and by agglutination and adsorption tests. Thirty-two days later the wife (case 41) of this patient had the disease, as proved by clinical, hematologic and serologic investigations. Retrospective analysis revealed a probable contact occurring either thirty-two days before or within seven days of the onset. Simultaneously, however, with the first case, a third member of the family, a son 2 years of age, had an illness consisting of an acute infection of the upper respiratory tract, fever and cervical adenitis, all of which were of short duration. Although it was not practicable to make confirmatory tests, this was presumably a case of mild infectious mononucleosis. The fourth member of the family, a girl 5 years of age, had a similar illness with the onset occurring several days after that of her brother. Unfortunately, confirmatory tests were not made in her case either. Epidemiologically the train of events suggested serial transmission of the disease through the two children to the mother, thus indicating infection by contact.

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14 Ramsdell, S. G., and Davidsohn, I. *J. Immunol.* **18** 473, 1930.

15 Bernstein, A. *J. Clin. Investigation* **13** 419, 1934.

16 Boveri, R. *Klin. Wchnschr.* **12** 666, 1933.

17 Deicher, H. *Ztschr. f. Hyg. u. Infektionskr.* **106** 561, 1926.

## SUMMARY

Sheep cell agglutinins in the serum of persons with infectious mononucleosis appear to be different from those in normal serum and those in the serum of persons with serum sickness

The sheep cell agglutinins in normal serum are adsorbed by guinea-pig kidney but not by beef cells, those in the serum of persons with infectious mononucleosis, by beef cells but not by guinea-pig kidney, and those in the serum of persons with serum sickness, by both guinea-pig kidney and beef cells

Evidence of infection by contact in cases of infectious mononucleosis is given

E G E Anderson of the Charles V Chapin Hospital assisted in this work

# COPPER AND IRON IN HUMAN BLOOD

## IV NORMAL CHILDREN

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AND

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In previous studies<sup>1</sup> of the copper and the iron content of the blood of adults in normal and in various pathologic states we have noted the important interrelationship which exists between these two elements. Especially interesting is the hypercupremia that accompanies anemia. Using the iron content of the blood as a means of estimating the hemoglobin content, we have demonstrated that hypoferronemia is associated with hypercupremia. We have extended our investigation to the blood in infancy and childhood. The present study encompasses an attempt to establish the normal ranges of copper and iron which are necessary for the proper interpretation of the changes in the blood in this age period.

## METHODS

The determinations of copper and iron were made during the months from September to December.

Venous blood was drawn from the sagittal sinus of patients less than 1 year of age and from the cubital vein of older subjects.

Blood of the new-born was obtained from the umbilical cord. We have included the five cases previously reported in a comparison of maternal and fetal blood<sup>2</sup> and the blood of another new-born infant. In each instance delivery was spontaneous.

The older subjects were chosen from a group of children at the St James Orphanage, in Omaha, who had been examined and found to be in good health.

Blood counts were made with standardized pipets and counting chambers of blood drawn by cutaneous puncture of the great toe or of the lobe of the ear.

Determinations of copper were made on 5 cc samples of blood by a method previously described<sup>1</sup>.

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Submitted for publication, Oct 30, 1935

From the Department of Medicine, Creighton University School of Medicine

1 Sachs, A, Levine, V E, and Fabian, A A. Copper and Iron in Human Blood. I Normal Men and Women, II Blood Copper and Iron in Men and Women with Various Pathologic Conditions, Arch Int Med 55 227 and 241 (Feb) 1935

2 Sachs, A, Levine, V E, and Fabian, A A. Copper and Iron in Human Blood. III Blood Copper and Iron in Pregnancy and in the New-Born, Arch Int Med 55 249 (Feb) 1935



*Values for Copper and Iron in the Blood of Normal Children*

Name	Sex	Age	Erythrocytes	Copper, Mg per 100 Ce	Iron, Wet Ashing, Mg per 100 Ce	Iron, Dry Ashing, Mg per 100 Ce	Hemo globin,* Gm per 100 Ce
1	M	New born		0 076	53 45		15 92
2	M	New born		0 071	43 65		13 03
3	F	New born		0 075	50 20		14 99
4	F	New born		0 098	50 00		14 92
5	M	New born		0 089	54 65		16 30
6	F	New born		0 091	58 80		17 55
7 All	M	1½ mo	4,590,000	0 152	34 15		10 18
8 Ste	M	2 mo	4,525,000	0 151	34 80		10 39
9 Mar	F	3 mo	3,365,000	0 159	32 25	32 00	9 63
10 Jos	M	3½ mo	4,790,000	0 186	32 50		9 70
11 All	M	7 mo	3,960,000	0 163	35 10	35 56	10 48
12 Jos	F	1 yr	4,520 000	0 190	38 60	38 80	11 52
13 Joh	M	2 yr	3,875,000	0 211	40 50	39 04	12 01
14 Jes	M	2 yr	3,815,000	0 239	32 60	32 00	9 73
15 Ger	M	2 yr	4,000,000	0 200	44 00	43 96	13 01
16 Art	M	2 yr	4,100 000	0 193	40 90	41 04	12 21
17 Jac	M	3 yr	4,000,000	0 250	40 00	40 00	11 94
18 Rob	M	3 yr	3,750,000	0 183	43 10	43 26	12 87
19 El	M	3 yr	4,115,000	0 186	37 00	37 36	11 05
20 Alb	M	3 yr	4,025,000	0 203	37 60	37 20	11 22
21 Mar	F	3 yr	3,940,000	0 182	35 70	36 36	10 66
22 Bil	M	4 yr	4,400,000	0 187	42 20	42 12	12 60
23 Jas	M	4 yr	3,800,000	0 160	43 30	43 32	12 93
24 Jos	M	4 yr	3,615,000	0 185	42 20	41 88	12 60
25 Len	F	4 yr	4,430,000	0 167	40 35	40 00	12 04
26 Pet	M	4 yr	4,025 000	0 177	40 10	39 60	11 97
27 Cat	F	5 yr	3,530,000	0 148	41 15	39 80	12 23
28 Ire	F	5 yr	4,340,000	0 173	41 65	41 68	12 43
29 Rat	F	5 yr	4,100 000	0 181	38 45	38 64	11 18
30 Phi	M	5 yr	3,850,000	0 167	40 50	41 88	12 09
31 Joh	M	5 yr	4,190,000	0 205	43 00	42 90	12 84
32 Joh	M	6 yr	3,815,000	0 175	42 35	42 32	12 64
33 Del	F	6 yr	3,840,000	0 182	42 35	42 12	12 70
34 Ral	M	6 yr	4,350,000	0 158	40 55	40 00	12 10
35 Art	M	6 yr	3,830 000	0 172	37 60	37 56	11 22
36 Ang	F	6 yr	4,230,000	0 169	41 65	41 24	12 43
37 Ire	F	7 yr	4,000,000	0 154	42 00	40 80	12 60
38 Owe	M	7 yr	3,900,000	0 182	39 70	40 00	11 85
39 Flo	F	7 yr	4,540,000	0 214	42 00	42 12	12 60
40 Ric	M	7 yr	4,100,000	0 164	40 80	41 04	12 18
41 Paul	F	7 yr	4,325,000	0 168	39 05	39 20	11 66
42 Vir	F	8 yr	4,575,000	0 160	41 50	41 54	12 39
43 Tho	M	8 yr	4,025,000	0 167	38 30	39 50	11 43
44 Cla	M	8 yr	3,540,000	0 181	37 75	37 45	11 27
45 Hel	F	8 yr	3,680,000	0 166	40 00	40 20	11 94
46 Cat	F	8 yr	3,400,000	0 164	36 90	36 36	11 01
47 Jea	F	9 yr	4,350,000	0 156	40 05	40 00	11 96
48 Nel	F	9 yr	3,680,000	0 165	41 85	42 43	12 49
49 Ann	F	9 yr	3,890,000	0 169	39 35	39 20	11 75
50 Joe	M	9 yr	4,040,000	0 169	39 20	37 20	11 70
51 Dor	F	9 yr	4,080,000	0 148	41 50	41 88	12 39
52 Cha	M	10 yr	3 980,000	0 181	41 85	42 32	12 49
53 Tin	F	10 yr	3,840 000	0 174	41 15	41 00	12 28
54 Kat	F	10 yr	3,850,000	0 175	38 75	38 76	11 57
55 Ton	M	10 yr	4,500,000	0 169	40 50	39 80	12 09
56 Rob	M	10 yr	4,500 000	0 169	42 45	42 76	12 67
57 Joh	M	11 yr	3,800,000	0 141	41 65	41 68	12 43
58 Wal	M	11 yr	3,940,000	0 159	43 85	42 76	13 09
59 Hel	F	11 yr	4,000,000	0 137	40 50	40 80	12 09
60 Don	M	11 yr	4,815,000	0 175	44 65	44 44	13 33
61 Ray	M	11 yr	4,040,000	0 180	43 45	42 96	12 97
62 Lil	F	12 yr	4,050 000	0 178	42 55	42 60	12 70
63 Mlk	M	12 yr	4,020,000	0 151	40 65	40 00	12 13
64 Bet	F	12 yr	4,000,000	0 141	41 85	42 32	12 49
65 Ant	M	12 yr	3,940,000	0 166	42 55	41 88	12 70
66 Wil	F	12 yr	4,215,000	0 174	41 65	41 24	12 43
67 Joe	M	13 yr	3,965,000	0 175	43 10	42 32	12 87
68 Mil	F	13 yr	4,350,000	0 162	43 30	43 24	12 92
69 Poe	M	13 yr	4,575,000	0 179	43 65	44 44	13 03
70 Mar	F	13 yr	4,420,000	0 165	42 75	42 76	12 76
71 Gab	M	14 yr	4,050,000	0 133	43 45	44 44	12 97
72 Eul	F	14 yr	4,090,000	0 174	43 85	43 24	13 09
73 Dor	F	14 yr	4,520,000	0 140	39 50	41 24	11 79
74 Vie	F	14 yr	3,770,000	0 163	44 25	44 20	13 21
75 Mar	F	14 yr	3,740,000	0 147	41 30	41 88	12 33
76 Mor	F	15 yr	3,850,000	0 157	44 25	43 72	13 21
77 And	F	15 yr	4,330,000	0 149	42 20	42 12	12 60
Average for new born				0 083	51 79		15 45
Average for infants from 1½ mos to 15 yrs of age				0 171	40 51		12 00

\* Hemoglobin =  $\frac{\text{milligrams of iron in 100 cc of blood}}{3.35} = \text{grams of hemoglobin in 100 cc of blood}$

Determinations of iron were made on 0.5 cc samples of blood by a modified Wong wet ashing method<sup>3</sup>. The results were checked on 5 cc samples of blood by a dry ashing method which we have devised<sup>4</sup>.

### IRON

The blood in infancy, especially during the first year of life, is characterized by a rapidly changing picture. Instead of a single standard for the hemoglobin content, such as is commonly employed for adults, it is preferable to use a standard curve which reflects the normal variations found in each age period. Several normal curves for hemoglobin have recently been reported from different parts of the world<sup>5</sup>.

There is no absolute agreement in the figures reported by the investigators whose results are included in chart 1. The well nourished patients in Williamson's<sup>5a</sup> series uniformly showed higher hemoglobin levels than the relatively anemic institutional subjects included in Mackay's<sup>5c</sup> report. When one takes into consideration the status of the subjects chosen with regard to birth weight, climatic conditions and social and economic conditions, as well as the differences in the methods used for making the determinations of hemoglobin, the curves all tend to conform to a definite configuration. For instance, all agree on the detail of the sharp decline of the hemoglobin content in the new-born that occurs immediately post partum, which was first described by Leichtenstein<sup>6</sup>. The time-honored explanation for this phenomenon ascribes the rapid hemolysis to a physiologic adaptation on the part of the new-born infant to its extra-uterine environment, where the availa-

3 Sachs, A., Levine, V. E., and Appelsis, A. Iron in Human Blood, *Arch Int Med* **52** 366 (Sept.) 1933.

4 Fabian, A. A., Sachs, A., and Levine, V. E. Comparison of Wet and Dry Ashing Methods for Determining Blood Iron, *Proc Soc Exper Biol & Med* **32** 662, 1935.

5 (a) Williamson, C. S. Influence of Age and Sex on Hemoglobin, *Arch Int Med* **18** 505 (Oct.) 1916. (b) Wilke, E. Ueber den Gehalt des Blutes gesunder Kinder vom zweiten bis vierzehnten Lebensjahr an roten Blutkörperchen, an Blutfarbstoff, an Retikuloeyten und an Thrombocyten, *Folia haemat* **52** 291, 1934. (c) Merritt, K. K., and Davidson, L. T. The Blood During the First Year of Life, *Am J Dis Child* **46** 990 (Nov.) 1933. (d) Kotikoff, I. A. Blood Iron in Nurslings in Normal and Pathologic Conditions, *Jahrb f Kinderh* **132** 180, 1931. (e) Mackay, H. M. M. The Normal Hemoglobin Level During the First Year of Life. Revised Figures, *Arch Dis Childhood* **8** 221, 1933. (f) Elvehjem, C. A., Peterson, W. H., and Mendenhall, D. R. Hemoglobin Content of the Blood of Infants, *Am J Dis Child* **46** 105 (July) 1933. (g) Drucker, P. Investigations on the Normal Values for the Hemoglobin and the Cell Volume in the Small Child, *Acta pædiat* **3** 1, 1923. (h) Kato, K., and Emery, O. J. Hemoglobin Content of the Blood in Infancy, *Folia haemat* **49** 106, 1933.

6 Leichtenstein, O. Untersuchungen über den Hämoglobulingehalt des Blutes in gesunden und kranken Zuständen, Leipzig, F. C. W. Vogel, 1878.

ble oxygen is at a higher tension Horváth and Hollósi<sup>7</sup> have recently demonstrated that polycythemia and an elevated hemoglobin level are not present in infants delivered by cesarean section and in those subjected to a minimum of trauma during labor Further study may clarify this problem and perhaps modify the accepted views

Although our series of determinations includes but six infants in the age group from birth to 1 year, we have charted the figures because they coincide with the results obtained by other investigators who have reported representative groups of figures for infants in this age period Our data conform with the precipitous drop in the hemoglobin curve

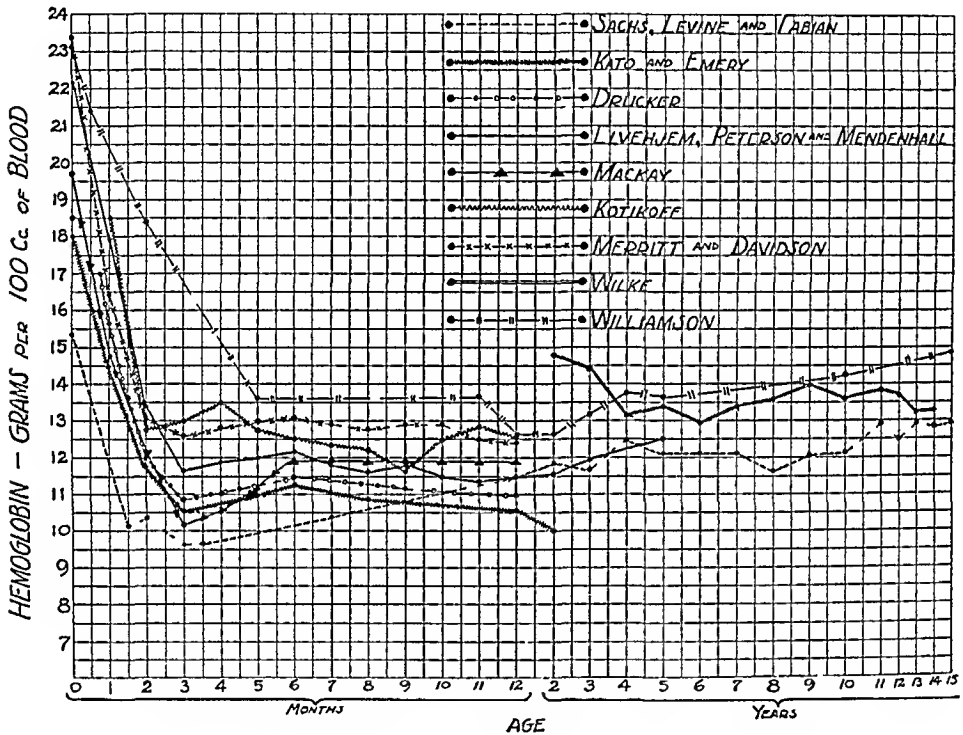


Chart 1—Hemoglobin values for the blood of normal children reported by various authors

observed by others in infants in the third month of life This secondary decline in the hemoglobin content is even less well understood than the original drop occasioned by postpartum hemolysis Is this a phenomenon due to a depletion of iron? If so, the condition should be amenable to treatment with prophylactic doses of iron administered soon after birth

The infant relies on its store of blood-building elements to supplement the anemia-favoring milk diet of the first year of life In premature infants the immediate administration of hematopoietic stimulants is imperative, since the opportunity to store these essentials has been

<sup>7</sup> Horváth, Z, and Hollósi, C Birth Pains and the Blood of the New-Born, *Am J Dis Child* 49 689 (March) 1935

denied in utero. The low hemoglobin values during the third month of life of a full term infant may represent either a depletion of the hematopoietic reserve or that point at which the adjustment is finally made in digestive and absorptive processes to insure utilization of the extrinsic supply of hematopoietic requirements.

After the first year of life the figures for hemoglobin show nothing unusual other than a gradual rise to the level for adults. Differences in hemoglobin values due to sex are not observed until after adolescence. The substantial difference in the average figures for the iron content for normal men and women necessitates the establishment of a separate standard for each sex.

We maintain that in children the use of a standard hemoglobin curve is preferable to a single standard. However, for clinical purposes, where percentage figures are in common use, a single standard must be set to represent 100 per cent hemoglobin. The figures for whole blood iron used to estimate the hemoglobin content demonstrate the need for a standard assigned specifically to children. Excluding the iron values for the new-born, the series of seventy-one specimens of blood listed in table 1 gives an average of 40.51 mg. per hundred cubic centimeters of blood. This represents the 100 per cent value for iron in infancy and childhood, which may be included in the following formula:

Milligrams of iron in 100 cc. of blood  $\times 2.5$  = hemoglobin—for children

Our average for a large series of normal men, 50 mg. of iron, and our average for normal women, 45 mg. of iron, per hundred cubic centimeters of blood, were incorporated in the following formulas:

Milligrams of iron in 100 cc. of blood  $\times 2$  = hemoglobin—for men

Milligrams of iron in 100 cc. of blood  $\times 2.25$  = hemoglobin—for women

Therefore, separate standards should be used for men, women and children.

Using the Butterfield<sup>8</sup> factor, iron = 0.335 per cent hemoglobin, the average for the seventy-one children in the present series was 12.09 Gm. of hemoglobin per hundred cubic centimeters of blood. In other words, a normal child would register only 80 per cent hemoglobin on the ordinary clinical hemoglobinometer, which uses one standard for comparison of all bloods regardless of the age or sex of the subject. Hemoglobinometers should be equipped so that the standard can be adjusted in dealing with men, women or children.

<sup>8</sup> Butterfield, E. E. Ueber die Lichtextinktion das Gasbindungsvermögen und den Eisengehalt des menschlichen Blutfarbstoffs in normalen und krankhaften Zuständen, *Ztschr. f. physiol. Chem.* 62: 173, 1909.

Although the iron method for hemoglobin determination has been recommended for its accuracy by many hematologists, some investigators challenge its use. Van Vyve,<sup>9</sup> who first reported a series of blood iron figures for the new-born, listed low values which showed no correlation with hemoglobin percentages as determined by one of the methods in use at the time. Taghamuro<sup>10</sup> reported similar results. The figures of Halfer<sup>11</sup> did not bear out the proportionality of blood iron to hemoglobin. Sobel and Dreker<sup>12</sup> found in 88 per cent of their cases that the iron method gave hemoglobin values from 5 to 15 per cent lower than those read on a Sahli hemoglobinometer.

With regard to those investigations carried on a few decades ago, one may justifiably question the accuracy of the methods employed for the determination of iron. In the more recent reports the discrepancy may be due to the use of clinical colorimetric hemoglobinometers which are not instruments of precision. Karshan and Freeman<sup>13</sup> compared the method for the determination of iron with the accepted oxygen capacity method for the determination of hemoglobin and found a close correlation of the figures obtained by the two procedures. Abt's recent report on blood iron in children likewise showed that a true proportionality exists between the amounts of iron and hemoglobin.<sup>14</sup>

In our previously reported studies of the iron content of human blood we employed a modified Wong wet ashing process. Burmester,<sup>15</sup> in his comparison of various iron methods, stated that the Wong procedure is not as well controlled as other related technics. We have had an opportunity in our present study to check the results obtained by the Wong method with a dry ashing process on a blood sample ten times as large. After the copper had been removed from the ash of a 5 cc sample of blood, the precipitate that remained was analyzed for its iron content. The figures obtained by the wet and dry ash methods listed in

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9 Van Vyve, G. Le fer dans le sang des nouveau-nés, Thèse de Paris, no 415, 1902.

10 Taghamuro, P. Contributo clinico-sperimentale sul contenuto in ferro del sangue dei bambini in condizioni normali e patologiche, *Pediatria* **15** 561, 1907.

11 Halfer, G. Blood Iron in Children in Normal and Pathologic Conditions, *Arch de méd d enf* **33** 659, 1930.

12 Sobel, I. P., and Dreker, I. J. Determination of the Iron Content of the Blood in Children, *Am J Dis Child* **45** 486 (March) 1933.

13 Karshan, M., and Freeman, R. G., Jr. Study of Hemoglobin Methods, *J Lab & Clin Med* **15** 74, 1929.

14 Abt, A. F. Anemia of Premature Infants. II. A Comparative Study of Blood Iron and Hemoglobin Values in Premature Infants, *Am J Dis Child* **49** 1204 (May) 1935.

15 Burmester, B. R. An Investigation of a Method for Iron Determination in Blood, *J Biol Chem* **105** 189, 1934.

table 1 showed close agreement. The percentage deviation for the whole series was about 1 per cent. This justifies the use of the rapid wet ash method for iron determination.

### COPPER

On the basis of the copper level in the blood of adults, 132 micrograms and 131 micrograms per hundred cubic centimeters of blood for normal men and women, respectively, the blood of the new-born by comparison showed hypocupremia. In the six cases included in table 1 the average value for blood from the fetal cord was 83 micrograms of copper per hundred cubic centimeters, or slightly more than one half the values for adults. We have previously attempted to assign an explanation for these findings.<sup>2</sup>

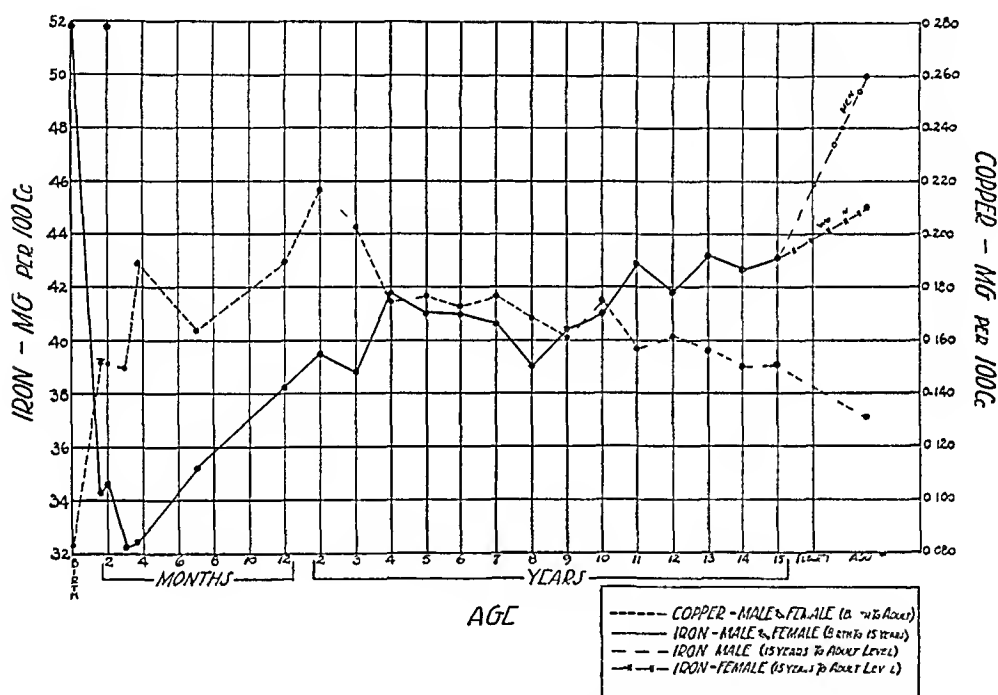


Chart 2—Copper and iron values for the blood of normal children

The copper content of the blood begins to rise immediately after birth, reaching a peak during the second year and gradually declining to the level for adults. The average for the seventy-one subjects, aged 1½ months to 15 years, was 171 micrograms of copper per hundred cubic centimeters of blood. This represented a distinctly higher level than that observed for adults. The figures for children, as in the case of those for adults, showed no variation due to sex.

The importance of establishing the normal copper range for children is apparent from an analysis of our previous data for adults. We have observed hypercupremia in anemia and in various other pathologic states. Were the normal standards for adults applied to children, the figures for the children would be designated hypercupremic. A reciprocal rela-

tionship of copper to iron has been observed in human blood. Since the level of the iron in the blood of children is 20 per cent lower than that in adults, the relationship is apparently maintained in the child, who presents a relatively hypercupremic picture. Further graphic evidence of this reciprocal relationship is noted in chart 2. The original hypocupremia of the new-born is associated with hyperferronemia. The trend of figures for each element is then observed to follow in an inverse pattern. The peak for blood copper is accompanied with a relatively low blood iron content. This is followed by a gradual approach of each element to the level for adults.

#### SUMMARY

The average iron content of the blood of the new-born in six cases was 51.79 mg per hundred cubic centimeters. The average hemoglobin content for this group was 15.45 Gm per hundred cubic centimeters.

The average iron content of the blood of seventy-one normal children aged from 1½ months to 15 years was 40.51 mg per hundred cubic centimeters. The average hemoglobin content for this group was 12.09 Gm per hundred cubic centimeters.

A separate hemoglobin standard must be set for children if the figures are expressed on a percentage basis. The formula  $\text{milligrams of iron in 100 cc of blood} \times 2.5 = \text{hemoglobin}$  is suggested as a means of estimating the hemoglobin content of the blood of children.

The average copper content of the blood of the new-born in six cases was 83 micrograms per hundred cubic centimeters.

The average copper content of the blood of seventy-one normal children aged from 1½ months to 15 years was 171 micrograms per hundred cubic centimeters.

Copper and iron maintain a reciprocal relationship in the blood of normal children.

# Progress in Internal Medicine

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## PERIPHERAL VASCULAR DISEASES

A REVIEW OF SOME OF THE RECENT LITERATURE AND A CRITICAL  
REVIEW OF SURGICAL TREATMENT

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A REVIEW OF SOME OF THE RECENT LITERATURE

By DR SCUPHAM

Since the publication of the review of the subject of peripheral vascular disease a year ago there have appeared a large number of papers. Many of them have been repetitions of previous work which, while adding but little new information, have served to clarify the subject and to confirm or contradict conclusions previously offered. Many such contributions are included, and it is hoped that all those which are particularly significant have been considered, although no attempt has been made to include all the papers on the subject.

### THE BLOOD VESSELS

In regard to the structure of the capillaries, Jones<sup>1</sup> is of the opinion that fundamentally they are no different from other blood vessels. They have an endothelial layer, a contractile system which consists of smooth muscle cells and a nerve supply. He differs from most previous observers in that he considers that the Rouget cells are not part of the contractile system but an essential part of their innervation.

Capps,<sup>2</sup> by means of the Hewlett and Van Zwaluwenburg plethysmograph, has demonstrated the existence of tone and has studied some

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1 Jones, Tudor. The Structure and Mode of Function of the Capillary Blood Vessels, *Am J Anat* **56** 227, 1936

2 Capps, Richard B. A Method for Measuring Tone and Reflex Constriction of the Capillaries, Venules and Veins of the Human Hand with the Results in Normal and Diseased States, *J Clin Investigation* **15** 229 (March) 1936



of its characteristics in the small vessels of the hand. He accepts as a definition of tone a resistance to stretch. The tone of these vessels as a group responds to a change of temperature as applied directly and locally. It is increased with a lower temperature and decreased at a higher one. In addition, the response can be demonstrated reflexly by the application of heat to the leg in the manner of Landis and Gibbon. It is to be noted that when the sympathetic nerve supply to the arm was interrupted there was an increase of blood flow into the hand. There was a marked decrease in the tone of the vessels with the local application of heat under such conditions, but there was no reflex response to the application of heat to the legs.

Capps showed that under all conditions, except after interruption of the sympathetic supply, there was a reflex vasoconstriction in these vessels to a noxious stimulus such as a pinch. This confirms the existence of smooth muscle walls with a definite nerve supply to the capillaries, venules and veins unless such an effect is entirely arteriolar.

In regard to the nerve supply, Kuntz<sup>3</sup> suggests an explanation for the failure to secure complete sympathetic paralysis in the upper extremity by extirpation of the inferior cervical ganglion and the first and second thoracic segments of the sympathetic trunk, including the second thoracic ganglion. He believes that there may be a sympathetic pathway within the spinal canal and suggests that small branches recurrent from the gray rami passing into the vertebral canal, which have been considered as terminating in the walls of blood vessels within the canal, may in fact extend along through the vascular plexuses and eventually unite with the brachial plexus. This has not been anatomically demonstrated in human beings but has been observed in cats.

Woollard<sup>4</sup> has a somewhat different explanation for the difference in the results of sympathectomy in the upper and in the lower extremities. He believes that normally the lower extremities have a much greater degree of constrictor tone. He bases this opinion on the observation that anesthetization of the nerves of the legs results in a greater rise in temperature than when the same procedure is carried out on the arms and hands. If the legs are placed in hot water, the skin of the hands quickly shows a rise of temperature, while when the arms are immersed a much longer time is required for a similar rise in surface temperature. Thus, if an increased constrictor tone is an inherent quality of the vessels of the leg, interruption of the nerve control will have less effect in releasing it.

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3 Kuntz, Albert. *The Autonomic Nervous System. Essential Anatomy*, J. A. M. A. **106** 345 (Feb. 1) 1936.

4 Woollard, H. H. *The Peripheral Sympathetic Nervous System*, Brit. J. Surg. **23** 425, 1935.

Scott,<sup>5</sup> in discussing arterial spasms, says that he believes that in extreme forms of increased vasoconstrictor tone which are distinctly abnormal the angiospasm may be sufficiently severe to result in thrombosis and gangrene. Lewis,<sup>6</sup> in making observations on the effect of ergot on the cock's comb, states that the effect of the drug is a marked constriction of the vessels which is not capable of being released by local warming. The constriction is not sufficient to stop the flow of blood, but after a certain length of time the nutrition of the vessel walls fails, stasis occurs with dilatation and thrombosis follows. The circulation is entirely obstructed, and gangrene results.

Scott<sup>5</sup> believes that arterial spasm may occur with organic disease of the vessel, but he points out that in thrombo-angitis obliterans, in which increased vascular tonus is frequent and often of high grade, the presence of arterial spasm can well be explained by the fact that the essential pathologic condition is an inflammatory process which includes both the vein and the nerve in their extent as well as the artery. It is because of the nerve irritation that the higher degrees of vascular spasm occur. In contrast to this, in arteriosclerosis the disease is degenerative and involves the arterial wall only. The collateral circulation is not affected by the local arterial disease unless all the vessels are similarly involved. Therefore, spasm is not to be expected, and it does not commonly occur. However, Harris<sup>7</sup> is of the opinion that arteriosclerosis is accompanied with sufficient arterial spasm in some cases to warrant sympathectomy. This is not the usual belief, but that some degree of increased vasoconstrictor tonus may frequently exist is not to be doubted.

Scott<sup>5</sup> also described minor grades of spasm of the Raynaud type in which there is great variation of intensity. There is no evidence to indicate that in persons with this condition Raynaud's disease eventually develops, and no line can be drawn to differentiate conditions of this type from the characteristic Raynaud paroxysm. The cause is obscure, and the complaint is usually of a variable sensitivity of the hands and fingers to cold.

Angiospasm may occur in many types of functional and organic nervous disorders and is variable in its manifestations. This is in corroboration of the observations of others, as reported last year.

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5 Scott, W J M. Arterial Spasm in the Extremities, *Ann Surg* **102** 331 (Sept) 1935

6 Lewis, Thomas. The Manner in Which Necrosis Arises in the Fowl's Comb Under Ergot Poisoning, *Clin Sc* **2** 43, 1935

7 Harris, R I. The Role of Sympathectomy in the Treatment of Peripheral Vascular Disease, *Brit J Surg* **23** 414, 1935

There is another group of conditions in which angiospasm occurs consecutive to trauma. There are two main types.

1 Local painful ischemic attacks, as in the Raynaud syndrome, in response to exposure to cold. This may be a reflex phenomenon associated with involvement of large or small nerves in scar tissue. Irritation of a peripheral nerve is the essential factor.

2 Painful osteoporosis or reflex traumatic arthritis. This usually involves the foot. There is an inflammatory-like reaction without infection which is regarded as circulatory in origin and angiospastic in nature, although, as described, the superficial circulation is increased. In roentgenograms the bones show the characteristic mottled osteoporotic appearance, and the cartilage between the small bones disappears. Periarterial sympathectomy gives some relief, but ganglionectomy has been more satisfactory. Some patients respond well to conservative treatment.

#### SURFACE TEMPERATURE

Bierman,<sup>8</sup> after making a study of the temperature of the surface of the skin, states that this temperature varies with that of the environment, with the temperature of the body (internal heat production) and with the condition of the skin and the structures beneath it. It also varies in different regions of the body at a comfortable environmental temperature. It is lower over superficial veins than over arteries. It is higher over muscles than over bones or tendons and is higher over an active than over an inactive organ. Stout persons have a much lower cutaneous temperature than thin persons. Symmetrical areas usually show a variation of 1 C or less but occasionally show marked variation under normal conditions.

The surface of the skin of the extremities has a lower temperature than that of the trunk and shows the greatest fluctuation with changes in the environmental temperature. With an increase in the internal production of heat or an increase in the environmental temperature the temperature of the surface of the extremities may reach that of the trunk and head. With exposure to cold it falls much more rapidly than that of the body surface.

By means of rapid and constant changes in the temperature of the surface of the body, the temperature of the interior is kept within narrow limits, there is a continual balancing between heat production and heat loss from the surface. Other factors influencing the temperature are age, changes in metabolism and psychic influences.

The variations when there is fever are of interest. When fever is induced by physical means, the normal temperature gradient disappears,

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<sup>8</sup> Bierman, William. The Temperature of the Skin Surface, *J A M A* 106 1158 (April 4) 1936.

so that all points tend to reach nearly the same level and the temperature of the surface of the extremities may reach a high level even before the internal temperature is elevated. The temperature gradient may then become reversed.

When the body supplies its own energy to create fever, as in the spontaneous development of fever or with the intravenous injection of typhoid vaccine, the temperature of the toes may remain low or may even fall to lower levels while the internal temperature rises. This is during the period of chill. After the internal temperature has become elevated the surface temperature of the extremities rises and remains elevated during the period of defervescence. For this reason Bierman thinks that when the objective of artificial fever is peripheral vasodilatation, it is more rational to produce fever by physical means, since the initial stage of vasoconstriction is avoided.

This agrees with the observations of Johnson, Osborne and Scupham,<sup>9</sup> who observed the effects of the various methods for the artificial induction of fever by means of the plethysmograph. They also found that for maximum vasodilatation in the fingers it was not necessary to raise the body temperature to the higher levels. Temperatures of from 100 to 102 F were sufficient when physical methods were employed. In fact, at higher degrees of temperature the vasomotor system became unstable, and the amount of peripheral vasodilatation, as measured by the finger plethysmograph, became variable.

When air heated to 100 F is applied directly by means of a thermostatically controlled hood to the extremities, the surface temperature of the toes rises to the same level as that of the forehead. If the venous return flow of a normal leg is subjected to obstruction, the temperature of the toes rises much more slowly and does not reach the level of that of the unobstructed leg, and likewise in cases of venous disease the temperature response to direct heating is less than normal. In persons with arteriosclerosis, however, the temperature response of the toes to direct heating may be greater than normal. In persons with thrombo-angitis obliterans the response may be normal or nearly so, because both arteries and veins may be involved. This observation may be of diagnostic value in making a differential diagnosis, if these findings are corroborated by other observers.

The direct application of cool air to the lower extremities rapidly causes a drop in the surface temperature of the toes. The response is delayed and diminished in the presence of arterial disease.

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9 Johnson, C. A., Osborne, S., and Scupham, G. W. Studies of Peripheral Vascular Phenomena. IV. The Effect of Artificial Fever on the Pulse Volume Changes of the Finger, *Am J M Sc* **190** 485 (Oct.) 1935.

Youmans, Akeroyd and Frank<sup>10</sup> used observations of the surface temperature to study the changes in circulation in the feet and legs with changes in posture and muscular activity. When a subject stood still there was a definite fall in temperature, which in most cases took place gradually until the minimum was reached. In some cases the fall was irregular or intermittent, and when the recumbent position was resumed a rise was again noted. These changes occurred regardless of the environmental temperature. When one leg was exercised and the other was quiet with the subject in a standing position, the fall in temperature occurred in both legs. The circulatory rate was measured and found to be longer with the subject in the erect posture than reclining, but in the moving leg often shorter than when the subject was reclining and consequently several times shorter than in the resting leg.

Heating of the forearms and hands was accompanied with a rise in the surface temperature of the toes with the subject erect which exceeded the drop in surface temperature which followed quiet standing.

#### INTERMITTENT CLAUDICATION

The importance of objective methods for the measurement of intermittent claudication has been recognized, and attempts have been made to furnish an accurate method. So far most of these have been on the basis of subjective sensations experienced by the patient.

Kisch<sup>11</sup> has employed a test which he calls a standard exertion test of intermittent claudication. It consists of a maximal bending at the ankle, knee and hip joint, so that the knee rests on the abdominal wall, followed immediately by complete extension of these same joints, the body of the patient being in a horizontal position. This exercise is repeated thirty times a minute. The number of times this standard exercise is performed before pain results is designated as the threshold value for claudication, and it varies greatly in different patients. If the value is high, Kisch assumes that the circulatory defect either is well compensated or has not progressed far, the converse is likewise true. A steady increase or decrease in the threshold value indicates improvement or exacerbation of the circulatory defect.

Realizing the importance of a purely objective method of measurement, Hitzrot, Naide and Landis<sup>12</sup> have devised what appears to be an excellent, reliable and purely objective graphic method of measure-

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10 Youmans, J. B., Akeroyd, J. H., Jr., and Frank, Helen. Changes in the Blood and Circulation with Changes in Posture. The Effect of Exercise and Vasodilation, *J. Clin. Investigation* **14** 739 (Nov) 1935.

11 Kisch, F. Zur funktionellen Diagnostik der Dysbasia (Claudicatio) intermittens, *Med. Klin.* **32** 273 (Feb 28) 1936.

12 Hitzrot, L. H., Naide, M., and Landis, E. M. Intermittent Claudication Studied by a Graphic Method, *Am. Heart J.* **11** 513 (May) 1936.

ment The basis of this method is that fatigue of the contracting muscles consistently precedes the pain of intermittent claudication The early loss of contractile power or amplitude of contraction in muscle deprived of an adequate blood supply is an objective phenomenon which can be recorded graphically The apparatus used is ingenious and records the contraction of the muscles of the calf, which are stimulated to contraction electrically at varying rates of stimulation and periods of rest A definite amount of work is performed at each contraction The records for normal subjects showed remarkable uniformity, both when the circulation was unimpaired and when it was artificially occluded Fatigue curves were made for the recorded observations on a group of normal subjects The pain of intermittent claudication did not appear at any time during the test, although some fatigue of the foot or leg developed in some instances The amplitude of contraction was found to decrease as much as 50 per cent after a two minute period of rapid stimulation During slow stimulation the amplitude remained constant Whatever fatigue developed during periods of contraction disappeared during routine rest periods, and the amplitude of contraction returned almost to the initial amplitude after each standard rest period Age did not affect the type of record In persons with general weakness after long confinement to bed there were lower amplitudes and mild sensations of fatigue but not the pain of claudication or the rapid drop of amplitude which occurred in persons with vascular disease With complete obstruction to the flow of blood, fatigue or pain with loss in amplitude occurred even during slow stimulation In the succeeding rest period there was no recovery With more rapid stimulation severe symptoms resulted, with a marked reduction in the initial amplitude and without recovery in the succeeding rest period At a rate of stimulation of 1 contraction per second intolerable pain developed after a few barely measurable contractions, and it was impossible to continue the test Symptoms and findings of muscular fatigue disappeared quickly after the blood flow was released Venous congestion at varying degrees favored the development of fatigue and amplitude Peripheral dilatation in a normal subject produced little or no change in the fatigue curve

Patients with arterial disease of the lower extremities were studied, with definite and constant findings in each instance The same intensity of stimulation produced an initial lower amplitude of contraction than in the normal subject The amplitude of contraction began to diminish earlier and declined more rapidly In the routine rest periods the recovery of muscle power was less complete, so that the fatigue curves showed a tendency to have a conspicuous downward slope The diminution in amplitude was associated with sensations of fatigue and pain, which often became so severe that the test could not be completed

When vascular occlusion had recently occurred, the severity of the fatigue and pain resembled that in a normal subject in whom the blood flow to the muscles of the calf was completely interrupted by a pneumatic cuff. Improvement in the findings occurred in two patients who were under treatment and who showed definite circulatory improvement. It seems that the principal value of the test will be as a means of measuring the improvement following therapy. In one of the two cases reported treatment was by suction and pressure, and in the other, by the administration of tissue extract. This test will be of considerable value in the differentiation of pain of other types which can be confused with that of intermittent claudication. The authors point out that muscle weakness or atrophy due to other than vascular causes also may produce abnormal curves. A certain amount of cooperation on the part of the patient is necessary for the obtaining of good records.

#### ARTERIOGRAPHY

Opinions regarding arteriography and its usefulness from a diagnostic standpoint are still somewhat at variance. Baumgartner<sup>13</sup> thinks that arteriography is essential to the diagnosis of obstructive arterial lesions. He emphasizes, as do many others, that the method is particularly important because it permits the estimating of the collateral circulation. It is apparent that his views confirm those of others that arteriography is particularly valuable for determining the site of amputation, as reported last year. Edwards,<sup>14</sup> from his own observations and from those of others, is of the opinion that arteriograms in cases of arteriosclerosis and of thrombo-angitis obliterans are sufficiently characteristic so that these two arterial diseases may be differentiated. In arteriosclerosis the arteriogram may show complete occlusion of the arterial segments, but in addition it shows eccentric filling defects in the other segments. These vessels show a tortuous course, and the collateral circulation is greatly increased. In a case of thrombo-angitis obliterans the arteriograms show a varying extent of thrombosis with smooth-walled segments of vessels above the occluded portions. The course of the vessels is less likely to be tortuous, and the collateral vessels, though increased in number, are fewer than in a case of arteriosclerosis.

Allen<sup>15</sup> has continued his observation on arteriography and has reported an arteriographic study of the collateral circulation in cases

13 Baumgartner, J. A. A Contribution on Arterial Obliteration. The Importance of Arteriography in Surgical Diagnosis and Treatment, *Deutsche Ztschr. f. Chir.* **244** 339, 1935.

14 Edwards, E. A. The Arteriographic Comparison of Thrombo-Angitis Obliterans and Arteriosclerosis, *New England J. Med.* **213** 616 (Sept 26) 1935.

15 Allen, E. V. How Arteries Compensate for Occlusion. An Arteriographic Study of Collateral Circulation, *Arch. Int. Med.* **57** 601 (March) 1936.

of thrombo-angitis obliterans. He states that the normal arteriogram, as described last year, is characteristic. The main arteries and their important branches are visualized, and short, small branches are to be seen normally, but the collateral circulation is not marked. The arteriogram of a patient with occlusive arterial disease shows a marked collateral circulation, and it is this compensatory circulation which prevents gangrene in many cases of occlusive disease. Allen describes the chief characteristics of collateral arteries. They have a turning and twisting course. They show variation in size in any selected area and purposeless crossing and recrossing. They often pursue a lateral course and have many anastomoses with each other. He is of the opinion that when arterial occlusion develops the arteries which become the collateral vessels are already in existence but increase in size as a response to a demand for increased function which arises as a result of occlusion of the main arteries. Arteriograms of limbs of living subjects show fewer vessels than arteriograms of amputated limbs. The reason for this, Allen believes, is that many vessels in the living subject may not be actually functioning at the time the arteriogram was made and are only called on to function when the circulatory demands are sufficiently great.

Contiades, Ungar and Naulleau<sup>16</sup> have studied the effect of various contrast mediums used in arteriography on the walls of the vessels. They conclude that no histologic lesions are produced in the arterial wall with colloidal thorium dioxide or organic iodine compounds. Yet they feel that the use of these substances is not without danger. There is always a decrease in the arterial pressure with the use of thorium dioxide. Vasomotor disturbances are common, particularly arterial spasm. The reactions are extremely variable in different subjects, some persons are sensitive and show marked vasospasm, often with pain, and others show little or no reaction.

#### THROMBO-ANGITIS OBLITERANS

In regard to the etiology of thrombo-angitis obliterans there has been little of importance added during the last year. The effect of tobacco and the part it plays in this disorder are still unsettled.

Trasoff, Blumstein and Marks<sup>17</sup> studied cutaneous reactions in a group of thirty-one proved cases of thrombo-angitis obliterans. With

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16 Contiades, X. J., Ungar, G., and Naulleau, J. *Recherches expérimentales sur l'action vasculaire des produits de contraste utilisés en artériographie. Application à l'interprétation et la prévision des accidents de l'artériographie*, Presse méd **43** 1630 (Oct 19) 1935.

17 Trasoff, Abraham, Blumstein, G., and Marks, M. *The Immunologic Aspect of Tobacco in Thromboangitis Obliterans and Coronary Artery Disease*, J Allergy **7** 250 (March) 1936.



a large number of tobacco antigens they found that the cutaneous tests showed 16 per cent positive results in the group of thirty-one proved cases. The authors do not believe that the reactions had a definite relationship to the disease but consider that the explanation of the effect of tobacco must be on a pharmacologic and not an allergic basis. They further obtained thirty-four positive results to tests with tobacco in forty-one allergic persons, and they point out that of the hundreds of allergic patients whom they have studied none had thrombo-angitis obliterans.

Friedlander, Silbert and Laskey<sup>18</sup> studied the effect of the injection of extracts of tobacco on albino rats. The tobacco extract was prepared in Ringer's solution and injected intraperitoneally every day, the amount being gradually increased. Thirty-three of the forty-eight male rats treated with injections of denicotinized tobacco had gangrene of the toes within from five to twelve weeks. None of the twelve female rats treated for from five to eighteen weeks showed this lesion. In ten male animals used as controls no gangrene developed. Primary microscopic studies of the vessels showed an inflammatory process. Six rats were subjected to the daily inhalation of smoke, but only one male animal showed lesions similar to those produced by the extract.

Two interesting points to be seen in this work are, first, that vascular lesions could be produced by the effect of tobacco and, second, that these vascular lesions could be produced only in male animals. Braeucker<sup>19</sup> reports a case of endarteritis similar to that of Buerger in which traumatism was the essential etiologic factor. He believes that there may be a constitutional factor which results in the characteristic picture when injury to the vessel wall occurs. This injury may be inflammatory, possibly related closely to rheumatic fever. In the cases which he reports he thinks the cause of the vascular injury was traumatism.

Rabinowitz and his associates<sup>20</sup> have continued the investigations of the relationship of disorders of lipid metabolism to thrombo-angitis obliterans. There are apparently two essential effects which may result from disturbances in the highly complex biochemical reactions of phospholipid metabolism. The first is direct, according to Rabinowitz, in altering the coagulability of the blood so that intravascular clotting results. The second is concerned with the relationship

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18 Friedlander, Mae, Silbert, S., and Laskey, N. Toe Lesions Following Tobacco Injections in Rats, *Proc Soc Exper Biol & Med* **34** 156 (March) 1936

19 Braeucker, W. Ueber die Ursache der Arterienentzündungen, *Munchen med Wchnschr* **82** 1186 (July 26) 1935

20 Rabinowitz, H. M., and Kah, Joseph. Relationship of Phospholipin Metabolism to Thrombo-Angitis Obliterans and Its Treatment, *Am J Surg* **31** 329 (Feb) 1936

of lecithin and cephalin in the physiology of muscle contraction and the relationship to intermittent claudication

They have found the phospholipin content of the blood to be increased in cases of thrombo-angitis obliterans, and choline appears in large quantities in the urine. The phospholipins are made up of lecithin and cephalin. Choline is the end-product of the metabolism of lecithin. Incidentally, the relative amounts of these substances in the blood were found to be constant. In normal subjects the ratio of lecithin to cephalin was 6:1, while in patients with thrombo-angitis obliterans it was found to be as low as 2:1. This alteration of the ratio results in a tendency to hemolysis and in addition hastens the coagulation process of the blood. There results intravascular clotting, which is so characteristic of the disease.

The level of the phospholipid substances in the calf muscles of patients with thrombo-angitis was about half that of the muscles of normal controls. The relationship of these substances to the physiology of muscles suggested that intermittent claudication might be the result of this abnormal state. The belief is expressed that pain of this type is not the result of ischemia but rises directly as the result of muscular exhaustion produced by abnormal muscle metabolism in which creatinine phosphate plays a most important rôle.

This is the substance which supplies the energy for muscle contraction. The authors state that the capacity of muscle cells for work depends wholly on the resynthesis and content of creatinine phosphate in the muscles. The phospholipins supply a considerable proportion of the phosphoric acid which is necessary to form the substances on which the physiology of muscle contraction depends. It is to be noted that an adequate supply of oxygen is necessary for this process. Cephalin speeds up the oxidation process. The rate is both absolutely and relatively increased in the plasma in cases of thrombo-angitis obliterans, and consistently low oxygen values for the venous blood were found, leading the writers to believe that excessive oxidation occurs in the tissues. Because of this a deficiency of oxygen rapidly develops with exercise. The resynthesis of glycogen from lactic acid is impaired, and the typical picture of muscle fatigue and intermittent claudication develops. There was found to be a direct relationship between the deficiency of oxygen in the venous blood and the severity of pain.

To complete the cycle of biochemical reactions, a theory is advanced which increases the importance of phospholipid metabolism. Creatinine is derived from choline, which is also derived from the phospholipids. The energy for this reaction is dependent in turn on the glycogen-lactic acid reaction. The large amount of choline found in the urine may then

be due to the failure of the completion of the cycle of biochemical reactions in the metabolism of muscle contraction

McGrath,<sup>21</sup> in studying experimental peripheral gangrene, used the method of Rothlin and Polak. Gangrene was produced in the tail of the albino rat by the use of toxic doses of ergotamine tartrate. The gross phenomenon consisted of successive changes in color, including pallor, cyanosis and gangrene. Microscopically the most marked change was proliferation and swelling of the intima. This was particularly marked in the small arterioles and arteries, where in some sections the lumens were almost completely occluded. To a lesser extent the veins and large ventral artery of the tail were involved. In this artery the presence of a thrombus attached to the intima was characteristic. Leukocytic reaction in the arteries and arterioles was not appreciable, but in the veins there were areas of marked thrombophlebitis. The walls of the veins, the thrombus and the perivenous tissues were all involved in an intense infiltration of polymorphonuclear leukocytes. No sex differences were revealed in the original experiments. Male rats were not protected from gangrene by the administration of estrogenic substance. In female rats, however, to which adequate doses of estrogenic substance were given gangrene did not develop under the same experimental conditions. McGrath feels that this curious phenomenon suggests the possibility that the failure of thrombo-angitis obliterans to become manifest in the female may be associated with a protective action of the estrogenic substance in the internal secretion of the ovary.

Yater and Cahill<sup>22</sup> reviewed the literature on ergot poisoning and report the case of a man, aged 94, to whom ergotamine tartrate had been given for the treatment of pruritus. Gangrene of the feet developed which necessitated amputation. The cause of the gangrene was found to be occlusion of the medium-sized arteries, the small arteries and the arterioles by severe constriction and thrombosis. Intimal proliferation may also play a rôle. The picture in this case was typical of ergot poisoning and did not resemble that of thrombo-angitis obliterans.

Gould, Price and Ginsberg<sup>23</sup> report the case of a middle-aged woman who received a total dose of 1 mg. of ergotamine tartrate subcutaneously. Coldness and pain developed in the legs, followed by a bluish mottling in the lower two thirds of the legs. Pulsations in the peripheral arteries

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21 McGrath, E. J. Experimental Peripheral Gangrene, *J. A. M. A.* **105** 854 (Sept. 14) 1935.

22 Yater, W. M., and Cahill, J. A. Bilateral Gangrene of the Feet Due to Ergotamine Tartrate Used for Pruritus of Jaundice, *J. A. M. A.* **106** 1625 (May 9) 1936.

23 Gould, S. E., Price, A. E., and Ginsberg, H. I. Gangrene and Death Following Ergotamine Tartrate (Gynergen) Therapy, *J. A. M. A.* **106** 1631 (May 9) 1936.

disappeared. Death occurred several days later. The essential observation, in addition to arteriosclerosis, was of marked arteriolar constriction.

*Pathology*—Lindenbaum and Kapitza<sup>24</sup> are of the opinion that migratory phlebitis always accompanies thrombo-angitis obliterans. It frequently precedes arterial involvement, and these authors think that the intensity and the spread of the inflammation in the veins indicate the severity of the process in the arteries. They divide the disease into three stages: stage 1, migratory phlebitis without symptoms or with irrelevant symptoms of involvement of the arteries; stage 2, migratory phlebitis with definite arterial impairment; and stage 3, migratory phlebitis with widespread thrombosis of the peripheral arteries.

The pathologic condition in the veins in the first stage consists of a fresh thrombus, with an inflammatory reaction in the wall, perivascular edema and leukocytic cellular infiltration. Small granulomatous nodules in which necrotic foci may appear begin to develop. Later, organization takes place in the thrombus. It is suggested that these granulomatous nodules are sometimes difficult to differentiate from tubercles. They contain large cells which become vacuolated and often contain fat as well as polymorphonuclear giant cells. A second type of focal reaction occurs in the thrombus itself with the formation of epithelioid giant cells and lymphocytic infiltration. This phase is followed by organization. The thrombus becomes infiltrated with lymphoid cells and histiocytes. The process goes on to obliteration of the lumen or recanalization, as in cavernous angioma. In some of the resected veins no thrombus was present, only a thickening of the intima which encroached on the lumen.

Jákí,<sup>25</sup> on the other hand, does not believe that thrombophlebitis migrans is always linked with thrombo-angitis obliterans. He believes that an infection of low virulence is the cause and that it is of the nature of an allergic reaction in which latent and infectious foci are most important. He prefers the term thrombophlebitis saltans to the one usually used. It seems apparent that other types of migratory phlebitis occur in addition to that associated with thrombo-angitis obliterans.

Friedlander, Laskey and Silbert<sup>26</sup> made observations on the blood volume of twenty-five patients who had undergone surgical removal of

24 Lindenbaum, I, and Kapitza, L. Zur Klinik und pathologischen Histologie der Buergerschen Form der Thrombo-Angitis obliterans, *Arch f klin Chir* **184** 413 (Jan 22) 1936.

25 Jakí, J. Ueber Thrombophlebitis migrans (saltans) und ihre Aetologie, *Zentralbl f Chir* **62** 2056 (Aug 31) 1935.

26 Friedlander, Mae, Laskey, Norman, and Silbert, S. Studies in Thrombo-Angitis Obliterans (Buerger). X. Reduction in Blood Volume Following Bilateral Oophorectomy, *Endocrinology* **19** 461 (July-Aug) 1935.

the ovaries and uterus A number of female cats were subjected to removal of both ovaries The average blood volume following operation showed a reduction of about 25 per cent from that of normal controls There was an elevation of the cholesterol and fibrinogen contents of the plasma and an increase in the viscosity of the blood The authors believe that some substance capable of influencing the blood volume is produced by the ovaries even after other physiologic functions have ceased The cats subjected to operation likewise showed a tendency to a reduction of blood volume

#### ARTERIOSCLEROSIS

Duff<sup>27</sup> has written an exhaustive review of the subject of experimental cholesterol arteriosclerosis He concludes that in rabbits and guinea-pigs cholesterol is responsible for the atherosclerotic changes which follow the feeding of this substance It has not been possible to obtain the same effect in other animals The characteristic sclerotic changes are preceded by preliminary alteration in the vessel walls which are probably dependent on the cholesterol feeding It is in these areas that the lipid deposits occur and the characteristic alterations take place Hypercholesteremia and saturation of most of the viscera with cholesterol also occur This disease, he believes, is not identical with arteriosclerosis in man There are three essential factors in the development of experimental cholesterol arteriosclerosis (1) cholesterol in the diet, (2) hypercholesteremia and (3) injury to the intima of the arteries He states that there is no valid reason for believing that hypercholesteremia is noted regularly in association with arteriosclerosis in man There is no evidence that a disturbance of the lipid metabolism participates in the etiology The initial stage in the development of human arteriosclerosis consists of local changes in the walls of the arteries which are responsible for the subsequent deposits of lipid material These changes follow some sort of injury to the vessel wall, the cause of which is not known After the initial local injury lipoids are deposited in the damaged intima, especially in the intercellular substances Macrophages engulf the lipid material The free lipid deposits probably stimulate the proliferation of connective tissue in the intima, and this effect plus the original injury produces a reparative fibrotic process The lipid deposits may prevent immediate healing, and consequently the lesions persist and progress In some instances the lipoids may slowly absorb and finally disappear, leaving only a fibrinous thickening of the intima

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<sup>27</sup> Duff, G L Experimental Cholesterol Arteriosclerosis and Its Relationship to Human Arteriosclerosis, *Arch Path* 20 81 (July), 259 (Aug) 1935

Meeker, Kesten and Jobling<sup>28</sup> studied the effect of iodine on experimental cholesterol arteriosclerosis in rabbits. Potassium iodide in large doses was fed for from one to three months to rabbits in which atherosclerosis had previously been induced by the prolonged feeding of cholesterol. It was found to have no effect on the rate or nature of the involution of the vascular lesions, but it did appear to retard the return of the cholesterol content of the blood to normal levels. The authors suggest that this retardation may be due to the mobilization of stored cholesterol from the tissues.

Blotner<sup>29</sup> reports a case of diabetic arteriosclerosis in which gangrene developed. It is his opinion that the excessive use of tobacco was the final factor in the precipitation of gangrene in this case and suggests that when the circulation is sufficiently impaired in cases of arteriosclerosis the excessive use of tobacco should be prohibited.

Sprague,<sup>30</sup> in a discussion of the etiology of arteriosclerosis in man, holds that in spite of the many objections that have been raised against the validity of experimental arteriosclerosis one cannot escape the fact that this demonstration is a most significant step, in that atherosclerosis has actually been produced and in its production has shown some analogy with the arterial degeneration so frequent in diabetes mellitus, in which a disturbance of cholesterol metabolism is a factor. Other foods, including alcohol, he believes, play no part unless excesses in diet may be of some importance. Tobacco likewise is not considered a factor. He notes that arteriosclerosis in youth and middle age is predominantly a disease of males. Of twenty-five patients 40 years of age or younger who had coronary thrombosis, all were men. Sprague finds a plausible theory for this and speculates on the possibility of an unknown endocrine factor. While hypertension may lead to vascular degeneration it cannot be considered the etiology of arteriosclerosis. That there are racial and possibly hereditary factors which result in premature vascular disease seems certain. The author concludes that no theory of the etiology is wholly satisfactory and that the cause of degenerative vascular disease is unknown. However, the boundaries of the problem are being progressively narrowed by the study of experimental arteriosclerosis and by the chemical analysis of the vessels, as well as by studies of the properties of colloidal gels and by studies in human biology.

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28 Meeker, D. R., Kesten, H. D., and Jobling, J. W. Effect of Iodine on Cholesterol-Induced Atherosclerosis, *Arch. Path.* **20** 337 (Sept.) 1935.

29 Blotner, Harry. Excessive Smoking as a Possible Precipitating Factor in Diabetic Gangrene, with a Case Report, *Ann. Int. Med.* **9** 987 (Jan.) 1936.

30 Sprague, Howard B. The Etiology of Degenerative Vascular Disease, *New England J. Med.* **213** 659 (Oct. 3) 1935.

Beck, Fowler, Koenig and Bowen<sup>31</sup> state that vascular disease is common in obese persons and a frequent cause of death in such subjects. They found that the calcification of the arteries of the lower extremities was demonstrable roentgenographically. This is an exceedingly common finding in older persons with uncontrolled diabetes, but in persons in the early stages of diabetes and in obese persons, some of whom are potential diabetic patients, it is essentially absent. There is no essential difference pathologically between the sclerosis that occurs in the older diabetic patients and that in persons with senile atherosclerosis.

#### ACUTE ARTERIAL OCCLUSION

Millar and Reid<sup>32</sup> have written an excellent review on the subject of embolism, including pulmonary as well as peripheral embolism. It is useless to attempt a review of this paper here.

McKechnie and Allen<sup>33</sup> have made a study of one hundred cases of embolism and thrombosis of the peripheral arteries at the Mayo Clinic. They do not differentiate entirely between thrombosis and embolism. They comment on the fact that pain is not the constant symptom which it usually is thought to be. It was frequently absent in their group of cases. In only 54 per cent of the cases was pain the initial symptom. Numbness, coldness and tingling were common, and loss of muscle power was occasionally prominent. Heart disease was the usual cause of embolism, while thrombosis most frequently resulted from arteriosclerosis. The cessation of symptoms may indicate eventual recovery or gangrene. When gangrene was definitely established the symptoms were less severe. In some cases in which gangrene did not develop the initial symptoms gradually merged into those of ischemic neuritis. The chief physical findings were absence of pulsation of the acral arteries, lowering of the surface temperature, pallor and loss or diminution of the reflexes, sensation and muscular strength. The pallor was of an unusual degree. Thrombophlebitis was the only condition which was considered to cause difficulty in making a diagnosis. The prognosis in this group of cases was not good. Gangrene developed in from 45 to 50 per cent of the cases. As the study of this group of patients dated back to 1924, the outcome for the entire group is not comparable to that for

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31 Beck, E. C., Fowler, J. G., Koenig, E. C., and Bowen, B. D. Vascular Disease in the Obese Diabetic and in Non-Diabetics. A Discussion of Arteriosclerosis as a Cause of Diabetes, *Ann Int Med* 9:662 (Dec) 1935.

32 Millar, W. M., and Reid, M. R. Present-Day Views on Embolism, *Internat Abstr Surg* 61:505 (Dec) 1935.

33 McKechnie, R. E., and Allen, E. V. Sudden Occlusion of the Arteries of the Extremities. A Study of One Hundred Cases of Embolism and Thrombosis, *Proc Staff Meet, Mayo Clin* 10:678 (Oct 23) 1935.

groups of patients who have the benefit of modern methods of treatment. Thrombosis, particularly that due to arteriosclerosis, seems to produce lesser degrees of gangrene than embolism. Treatment should be initiated promptly. The use of local heat, particularly uncontrolled heat, such as the use of a hot water bottle, is dangerous because tissue deprived of its normal blood supply tolerates excessive heat poorly. Opiates should be used for the control of pain, and alcohol is an important and valuable drug. The limb should be protected from the slightest injury, and the temperature of the arm should not exceed 105 F. The authors advise the use of papaverine hydrochloride intravenously in amounts of  $\frac{1}{2}$  gram (0.03 Gm.). Improvement will follow within a few minutes if this drug is effective. General or spinal anesthesia may be used in selected cases for securing maximum peripheral vasodilatation. The use of intermittent negative and positive pressure is also advised but will be discussed later.

McIlhenny and his associates<sup>34</sup> emphasize the necessity for accurate, early diagnosis and the prompt institution of treatment.

Clute<sup>35</sup> reports two cases of acute arterial obstruction resulting from arteritis. Following the point of view of Leiche, he states that in cases of acute arteritis some signs and symptoms will develop which are due to the loss of blood supply and others will appear because of constant stimulation of the vasomotor sympathetic nerve fibers in the artery. Acute arteritis may arise during the course of an overwhelming general infection, such as septicemia or pneumonia. This type of arteritis is usually a terminal event. It may occur also, as in the two cases reported, as a localized arterial infection in the arterial wall. Focal infection may be the etiologic factor. Trauma is another factor which needs consideration. The onset of symptoms of acute arteritis is gradual. Weakness of the extremity is worse after exercise and is often an early symptom. The limb becomes cold and may become blanched. Cyanosis and excessive sweating may be noted. On examination pulsation in the involved artery is absent, and the vessels can be felt as a cord which is sometimes tender. Blood pressure readings are not obtainable. Changes in sensation, atrophy of the muscles and trophic ulcers may occur. Pathologic study following resection of a portion of the vessel in some cases showed periarteritis with thrombosis. Smears and cultures revealed no significant observations. Early operative treatment with resection of a portion of the artery is recommended, this procedure was successful in both the cases reported.

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34 McIlhenny, R. A., McIlhenny, R. C., and Voldeng, K. E. Embolism of the Extremities, *J. Kansas M. Soc.* **16** 450 (Nov.) 1935.

35 Clute, Howard M. Acute Arterial Obstruction from Arteritis, *New England J. Med.* **214** 137 (Jan. 23) 1936.



## SPECIFIC AND NONSPECIFIC TYPES OF ARTERITIS

Periarteritis nodosa is being reported with increasing frequency Middleton and McCarter<sup>36</sup> have recently reported three cases, in males This sex predominates in all reports The age incidence covers a wide range—from 3 months to 71 years The authors believe that the incidence of the disease clearly exceeds its clinical and pathologic recognition It seems to be closely associated with the group of rheumatic diseases

Bernstein<sup>37</sup> describes a case of periarteritis nodosa without peripheral nodules, diagnosed by biopsy The patient's illness was characterized by weakness, emaciation, fever, peripheral neuritis, abdominal pain, edema, amblyopia, tachycardia, eosinophilia and changes in the urine The author comments on the fact that the disease is probably not as uncommon as the cases reported on indicate

Volland<sup>38</sup> describes a case in a woman, aged 61, who had a syphilitic aortic aneurysm The small arteries of all the organs showed the picture of periarteritis nodosa, in addition, atypical amyloid degeneration occurred in the media and adventitia of the small arteries and in the cardiac muscle Volland questions the relationship of this disease to syphilis and considers the possibility of an allergic etiology

Knauer<sup>39</sup> describes the case of a patient who died of pulmonary tuberculosis and who had an abdominal aneurysm The typical picture of healed periarteritis nodosa was demonstrated in the lung The author is of the opinion that syphilis had nothing to do with the arterial disease

Mainzer and Joel<sup>40</sup> report a typical case of periarteritis nodosa which began as an infection of the throat During a course of three years *Streptococcus viridans* was present in blood cultures, and it was noted also at autopsy The authors believe this to be a streptococcal infection Motley<sup>41</sup> has described a case in which the important features were generalized involvement of a somewhat migratory character involving the vessels of both the upper and the lower extremities, the skeletal muscles and the kidneys, with symptoms of coronary disease, severe abdominal pain, bloody diarrhea, peripheral neuritis and cough with blood-streaked sputum There was marked leukocytosis and an

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36 Middleton, W S, and McCarter, J C The Diagnosis of Periarteritis Nodosa, *Am J M Sc* **190** 291 (Sept) 1935

37 Bernstein, A Periarteritis Nodosa Without Peripheral Nodules Diagnosed Antemortem, *Am J M Sc* **190** 317 (Sept) 1935

38 Volland, W Periarteritis nodosa mit atypischer Amyloidose nach luischer Infektion, *Beitr z path Anat u z allg Path* **96** 81 (Nov 18) 1935

39 Knauer, Bernhard Ueber einen Fall von vollkommen abgeheilter Periarteritis nodosa, *Centralbl f allg Path u path Anat* **63** 161 (Aug 30) 1935

40 Mainzer, F, and Joël, W Periarteritis Nodosa as a Manifestation of Sepsis Lenta Due to *Streptococcus Viridans*, *Acta med Scandnav* **85** 397, 1935

41 Motley, L Periarteritis Nodosa, *J A M A* **106** 898 (March 14) 1936.

eosinophil count as high as 28 per cent. The diagnosis was made during life, and the patient was treated with repeated blood transfusions, small doses of neoarsphenamine, a diet rich in vitamins and general symptomatic measures. There was apparent recovery.

Krahulk, Rosenthal and Laughlin<sup>42</sup> report an additional case, in which the widespread vascular lesions of necrotizing panarteritis occurred in a girl aged 9 years. The unusual feature in this case was subacute leptomeningitis.

Barker and Baker<sup>43</sup> describe another type of obscure arteritis under the term of proliferative intimitis of the small arteries. The outstanding clinical features that are mentioned in connection with this case are marked livedo reticularis, recurrent indolent ulceration, acute occlusion of the small arteries of the toes and severe intractable pain. Extensive proliferation of the intima and definite perivascular fibrosis in many of the small arteries and veins were noted. In some of the vessels the lumen was closed with a fibrous mass. Associated with this was marked periarterial fibrosis. This seemed to be a late stage of the disease. Many of the arterioles had thick walls with small lumens surrounded by irregular areas of fibrous tissue. There was no evidence of tuberculosis or syphilis, and the authors were unable to suggest any etiologic agent.

#### RAYNAUD'S DISEASE

Just where the line can be drawn between the typical Raynaud paroxysm and the so-called vasomotor neurosis of the same type is impossible to determine. Certainly many of the vasomotor neuroses, especially those precipitated by cold or emotion, although not typical of Raynaud's disease, are disorders of the same type. Although these minor disorders never seem to progress, their etiology is no more definite than that of Raynaud's disease.

Peet and Kahn<sup>44</sup> have published reports on a group of patients exhibiting vasomotor phenomena which they feel were allied to the Raynaud syndrome. In all cases there was evidence of organic disease. In one patient there was a tumor of the hypothalamus, which they believe was the cause of the vasomotor disturbance. The second patient showed a constant vasoconstrictor spasm involving both legs. This was relieved by ganglionectomy. Microscopic examination of the ganglion showed inflammatory reaction in the cells and other evidences of chronic

42 Krahulk, L., Rosenthal, M., and Laughlin, E. H. Periarthritis Nodosa (Necrotizing Panarteritis) in Childhood with Meningeal Involvement, *Am J M Sc* **190** 308 (Sept.) 1935

43 Barker, N. W., and Baker, T. W. Proliferative Intimitis of the Small Arteries and Veins Associated with Peripheral Neuritis, Livedo Reticularis and Recurring Necrotic Ulcers of the Skin, *Ann Int Med* **9** 1134 (Feb.) 1936

44 Peet, Max Minor, and Kahn, Edgar A. Vasomotor Phenomena Allied to Raynaud's Syndrome, *Arch Neurol & Psychiat* **35** 79 (Jan.) 1936

inflammation The authors cite the case of another patient, reported by Bennet and Poulton, who had vasomotor paroxysms in the hands that were typical of Raynaud's disease Autopsy later revealed a large carcinoma of the stomach, and examination of the inferior cervical ganglion, removed at operation, revealed carcinomatous metastases In the third case described by Peet and Kahn there were definite vasomotor changes in the legs and hands—both abnormal vasoconstriction and vasodilatation The definite lesion of the spinal cord, which was a meningocele, was removed at operation Apparently complete cure resulted In the fourth case fracture of the skull resulted in extensive cortical injury, and there were marked vasomotor disturbances which consisted of symmetrical cyanosis involving the trunk For a short distance below the cyanosed area the skin was completely blanched These observers believe that it is probable that in some cases of the Raynaud syndrome the smooth muscle of the smaller blood vessels has abnormal irritability Further, it is thought that in some cases so-called typical Raynaud's disease may be caused by the same factors which underlie hysteria The authors' final conclusion is that Raynaud's disease is merely a syndrome, since it can be caused by an exciting factor, pathologic or functional, located anywhere from the cerebral cortex throughout the various nerve pathways and even in the peripheral vessels themselves The cases described are not of Raynaud's disease but of typical vessel spasm resulting from central or peripheral nerve irritation

Kraetzer <sup>45</sup> advances the unique idea that the retention of arsenic in the body in certain cases may be the toxic factor responsible for Raynaud's disease In proof of this he cites seven cases of a more or less typical Raynaud syndrome in which retention of arsenic was demonstrable Six of these were in females and one in a male There was an increase in the urinary output of arsenic in all of them following the intravenous injection of sodium thiosulfate This was the only treatment instituted, and after its continuation for a variable period all the patients showed relief from symptoms and marked improvement in the general health The history of the onset of symptoms was variable, usually syncope of one or more fingers ushered in the complaint Later the spasm in almost all cases became widespread and in many of them was typical of the Raynaud paroxysm

Johnson and Hedges <sup>46</sup> studied the circulation in a case of Raynaud's disease complicated by scleroderma and sclerodactylia Their conclusions

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<sup>45</sup> Kraetzer, Arthur F Raynaud's Disease An Hypothesis as to Its Cause, New York State J Med **35** 1 (Nov 15) 1935

<sup>46</sup> Johnson Carl A, and Hedges, Robert N Studies on Peripheral Vascular Phenomena IV Finger Volume Changes in a Patient Showing Raynaud's Phenomena, Surg, Gynec & Obst **60** 1077 (June) 1935

were as follows. The circulation was persistently less than normal in the fingers even in the absence of paroxysm. Peripheral dilatation can be induced by the local application of heat, and during the cyanotic stage of these paroxysms the circulation is increased. The use of insulin-free pancreatic extract resulted in improvement in the color of the fingers but did not produce vasodilatation.

Pearse<sup>47</sup> found that in cases of Raynaud's disease, even when the hands were kept warm, cooling of the body caused the appearance of a paroxysm. Warming the body relieved the attack, but the converse also was true. Warming the body did not prevent an attack if the hands were exposed to cold. The author concluded that regulation of the body heat has a definite effect on the paroxysm of Raynaud's disease. This is confirmatory evidence that normal forms of stimulation produce an exaggerated vascular reaction. The local abnormality causes the excessive spastic response from a number of diverse motivating factors.

#### ACROCYANOSIS

Concerning the subject of acrocyanosis relatively little interest has been aroused. This is no doubt due to the fact that this disorder causes little or no disability, in fact, many persons who have the disorder make no complaint of their symptoms.

Elliott, Evans and Stone<sup>48</sup> made a careful study of one case of unusually severe acrocyanosis and made observations on two cases in which the symptoms were milder. Their conclusions as to the fundamental vascular defect are at variance with those of Lewis and Landis, but the authors agree in some respects. The larger arteries, including the digital arteries, were found to be intact, as were the larger veins. These authors disagree with Lewis and Landis that arteriolar constriction is the essential defect. They are convinced that there are a loss of tone and a loss of normal reactivity to stimulation of the small superficial vessels of the skin, namely, the capillaries and the collecting venules. The authors agree, however, that arteriolar constriction resulting from exposure to cold will intensify the symptoms by diminishing the inflow to the superficial vessels. The arguments that they have advanced are convincing. However, it does not seem reasonable that acrocyanosis, as they think, should not be regarded as a disorder that is secondary to disease elsewhere in the body, as almost all previous workers have considered it to be.

47 Pearse, H. E., Jr. Influence of Heat Regulatory Mechanism on Raynaud's Disease, *Am Heart J* **10** 1005 (Dec.) 1935.

48 Elliott, A. H., Evans, R. D., and Stone, C. S. Acrocyanosis. A Study of the Circulatory Fault, *Am Heart J* **11** 431 (April) 1936.

Capps<sup>2</sup> studied acrocyanosis in two cases with a plethysmograph. An abnormal absence of tone of the capillaries, venules and veins was noted. His findings are in agreement with those of Elliott, Evans and Stone that this loss of tone in the vessels on the venous side coupled with a slow arterial inflow at low temperatures is probably the explanation of the clinical features of the disorder.

#### ERYTHROMELALGIA

Mühlbacher<sup>49</sup> describes erythromelalgia as occurring in healthy men and women in attacks of burning pain at night, usually in the feet, lasting for a few hours and ceasing only to return again the next night. It seldom occurs during the day. Its cause is some disturbance for which no pathologic basis can be demonstrated in the vasomotor system, in the cerebral centers or in the ganglions. Elevation and rest afford some relief. Many types of treatment have been employed, but they are usually temporarily helpful, the symptoms sooner or later recurring. The author has tried insulin-free pancreatic extracts and the intravenous injection of calcium with some benefit. Ergotamine tartrate in small doses in combination with belladonna also is advised. Nothing further has been added to clarify this obscure condition.

#### EFFORT THROMBOSIS

Effort thrombosis has been reported in the last year with increasing frequency from many sources. That it is a definite clinical entity cannot be doubted, although the exact reason that thrombosis develops is still obscure. Little has been added to the clinical picture previously described. While in most of the cases the condition has involved the axillary vein or other veins of the upper extremities, Kux<sup>50</sup> reports four cases of traumatic thrombosis of the leg. These were all the result of direct trauma or excessively strenuous work. The clinical picture was the same in all cases. Swelling of the extremity, with paresthesias, coldness, fatigue and bluish-red discoloration was outstanding. The superficial veins presented a cordlike appearance. The author divides the condition into two types. The first is a purely thrombotic type and results from a tear or injury to the intima of the vein. In the second type, which he believes is due to overexertion, thrombosis follows as the result of hindrance to the flow of blood. Rossel<sup>51</sup> states that the arm is most often affected, particularly the arm which is more frequently

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49 Mühlbacher, W. Ueber Erythromelalgie und deren Behandlung, *München med Wchnschr* 82 1242 (Aug) 1935

50 Kux, E. So-Called Traumatic Thrombosis in the Arm and Axillary Vein, *Beitr z klin Chir* 161 286, 1935

51 Rossel, E. So-Called Traumatic Thrombosis of the Axillary Vein, *Svenska läk-tidning* 126 935, 1935

used Effort thrombosis occurs in young persons with good muscular development The author thinks the prognosis is good under conservative treatment

Robinson<sup>52</sup> describes two cases of primary thrombosis resulting from excessive muscular effort which involved the thoraco-epigastric artery of the right side In one patient the condition developed after he had been digging in the garden, and in the other after he had moved some heavy furniture The symptoms were pain in the side of the chest and the presence of a firm, tender cord A stringlike band could be felt under the skin running up from the costal margin and disappearing in the axilla Robinson believes the thrombosis to be the result of injury to the intima of the vein during the contraction of the underlying muscles It is possible that axillary thrombosis may originate in this vein, the primary thrombosis being overlooked because of the major condition affecting the axillary vein

McClanahan<sup>53</sup> reports the case of a muscular boy of 17 years He points out that the initial attack may be somewhat mild but that continuation of the use of the arm will result in much more severe involvement The arm should be allowed to rest until adequate circulation has been established

Veal and McFetridge<sup>54</sup> have reported two cases of primary thrombosis of the axillary vein The clinical history corresponds to that usually described Venography in these cases revealed the location of the obstruction clearly, and in a case in which the obstruction had existed for a long time there was an extensive collateral circulation The authors believe the cause to be trauma plus some anatomic predisposing factor Hyperabduction and external rotation of the shoulder seem to be important factors Obstruction usually occurs where the vein crosses the subcapularis muscle

#### TREATMENT

In the treatment of peripheral vascular disease the principal advances in the past year have been the correlation and crystallization of ideas and the application of the various methods more definite to each type of disease It has again been emphasized that peripheral vascular

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52 Robinson, R H O B Thrombosis Following Strain, *Brit J Surg* **23** 241 (Oct) 1935

53 McClanahan, B V Primary Thrombosis of the Axillary Vein, *Am J Surg* **30** 459 (Dec) 1935

54 Veal, J R, and McFetridge, E M Primary Thrombosis of the Axillary Vein An Anatomic and Roentgenologic Study of Certain Etiologic Factors and a Consideration of Venography as a Diagnostic Measure, *Arch Surg* **31** 271 (Aug) 1935

disease is a local manifestation of a general disease Barker<sup>55</sup> again asserts that in spite of the many warnings the vulnerability of the toes of patients with occlusive arterial disease has not been sufficiently emphasized. Gangrene is induced by the most trivial type of injury. In 35 per cent of a series of one hundred and seventy-one cases of thrombo-angitis obliterans with gangrene, this condition followed various therapeutic procedures, while in 39 per cent of one hundred and fifteen cases of arteriosclerosis with gangrene, therapeutic procedures were the cause. The author strongly recommends that no local, surgical or medical treatment of the toes be instituted in any case until the arterial blood supply has been proved adequate.

De Takats<sup>56</sup> in a report of five cases of acute arterial occlusion states that striking improvement in the circulation often follows the intravenous use of papaverine hydrochloride. If this drug is to be of any benefit it must be given as soon as the diagnosis of pulmonary or peripheral embolism is made. The intravenous injection of papaverine is a harmless procedure and can be available at all times, whereas other methods of treatment are often impossible outside of a well equipped hospital. As previously reported, the effect is prompt if any benefit is to be obtained. No stable solutions of papaverine are available. The author points out that the drug can be kept on hand in capsules and that solutions can be quickly made and sterilized by boiling. The principal effect of combating the reflex vessel spasm of arterial occlusion deserves the widest recognition. In embolism of the peripheral vessels papaverine used in combination with controlled heat and negative pressure has given excellent results.

Acetyl-beta-methylcholine is reported on again by Grace Goldsmith,<sup>57</sup> who states that it has three important actions: a parasympathetic stimulating effect, a vasodilating effect and a nicotine-like effect, which causes a rise in the blood pressure when its other actions have been abolished by atropine. Schwab and his associates<sup>58</sup> state that although primarily exerting its effect on the craniosacral division of the vegetative nervous system, it also produces vasodilatation of the peripheral arterioles, presumably by inhibition of the sympathetic constrictors. These investigators considered the possibility that this effect is due to stimulation of the parasympathetic vasodilator fibers, provided such fibers exist.

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55 Barker, N. W. The Danger of Gangrene of the Toes in Thrombo-Angitis Obliterans. *J. A. M. A.* **104** 2147 (June 15) 1935.

56 de Takats, Geza. The Use of Papaverine in Acute Arterial Occlusions, *J. A. M. A.* **106** 1003 (March 21) 1936.

57 Goldsmith, Grace A. The Effectiveness of Acetyl-B-Methylcholine Given by Mouth as a Vasodilating Agent, *Ann. Int. Med.* **9** 1196 (March) 1936.

58 Schwab, Edward H., Marr, W. L., and Moore, Robert M. Clinical Studies on the Action of Acetyl-Beta-Methylcholine Chloride. *Texas State J. Med.* **31** 574 (Jan.) 1936.

Goldsmith studied the effects of the oral administration of the drug and found a rise in the temperature of the skin to be usual. This rise was greatest in cases of hypertension and of Raynaud's disease. In cases of these conditions doses of 50 mg. were often effective, whereas in cases of arteriosclerosis and thrombo-angitis obliterans from 1,000 to 1,500 mg. was needed to produce significant vasodilatation. There was marked variability in the rise of the surface temperature in the various digits in cases of Raynaud's disease. In one case the rise in the temperature of the fingers varied from 19 C (35 F) in one digit to 89 C (16 F) in another. Organic occlusion of smaller vessels was thought to be the reason for this variation. Patients with hypertension and control subjects showed a uniform rise in temperature in all the digits. The action of the drug began from fifteen minutes to two and one-half hours following its oral administration. The duration of the rise in cutaneous temperature varied from one to six hours. By giving another dose of 1,500 mg. in three or four hours vasodilatation could be maintained for seven or eight hours. In three cases of thrombo-angitis obliterans a comparison was made with the vasodilating effect of typhoid vaccine given intravenously. Acetyl-beta-methylcholine was found to have 75 per cent of the vasodilating effect of artificially induced fever. The administration of this drug failed to relieve any of the severe grades of pain in cases of occlusive disease of the blood vessels, nor was any definite effect noted in cases of intermittent claudication. The effect on the pulse rate and the blood pressure when the drug was given by mouth was variable and not significant, in contrast to the effects of the subcutaneous administration, after which the blood pressure, heart rate, sweating, salivation and nausea were often increased.

Goldsmith concludes that this drug seems to be promising for use in cases of peripheral vascular disease because of its vasodilating properties, its prolonged action, the safety in its use and the ease of its oral administration. It seems, however, that its principal use may be found in Raynaud's disease or other conditions in which there is marked spasm of the smaller arteries. Schwab and his associates<sup>58</sup> agree in this. They found striking increases in the temperature in cases of Raynaud's disease. Some of the digits showed a rise of as much as 10 C (18 F), with pronounced systemic relief.

McGovern, McDevitt and Wright<sup>59</sup> studied the effect of theobromine with sodium salicylate as a vasodilator. They concluded that this drug is unreliable and too feeble a vasodilator to be useful in the treatment of peripheral vascular disease.

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59 McGovern, Teresa, McDevitt, Ellen, and Wright, Irving S. Theobromine Sodium Salicylate as a Vasodilator, *J. Clin. Investigation* **15** 11 (Jan.) 1935.



Lehman<sup>60</sup> has applied elevation of the environmental temperature in one case of acute arterial spasm. He suggests that this may have definite therapeutic possibilities.

Samuels'<sup>61</sup> monograph on the diagnosis and treatment of peripheral vascular disease is limited to a discussion largely of thrombo-angitis obliterans. The author again emphasizes the value and describes in detail the technic of treatment with hypertonic solutions of sodium chloride.

Silbert<sup>62</sup> has reviewed his experience of ten years with the treatment of thrombo-angitis obliterans by intravenous injections of hypertonic solution of sodium chloride. There is no essential change in his views, and certainly the results which he has obtained have been gratifying.

The center of interest in peripheral vascular disease during the past year has been in treatment with positive and negative pressure. There is still no unanimity of opinion in regard to the usefulness of this method under all conditions. The original workers have apparently had much more success than have others. Herrmann,<sup>63</sup> in an excellent monograph recently published, describes the history of various methods of treatment with positive and negative pressure over the past hundred years and their development to the present state. He describes in detail the application of this plan of treatment of the various types of vascular disease and gives an excellent résumé of other methods of treatment, together with the physiology and pathology of vascular diseases. Reid and Herrmann<sup>64</sup> state that the most startling results have been obtained among patients who are suffering from more or less sudden occlusion of the major arterial pathways to an extremity. The results in the treatment of the acute crises of peripheral vascular accidents have been the most thrilling observation in their clinic for many years. In every instance of acute obliteration of a major artery in which there was no obvious death of tissues, they were able to relieve the spasm and draw blood into the extremity in a short time, with quick relief from pain and

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60 Lehman, Edwin P. A Suggestion for Simple Treatment of Acute Arterial Spasm, *Am J M Sc* **190** 459 (Oct) 1935

61 Samuels, Saul S. The Diagnosis and Treatment of Diseases of the Peripheral Arteries, New York, Oxford University Press, 1936

62 Silbert, Samuel. Thrombo-Angitis Obliterans (Buerger). XI Treatment of Five Hundred and Twenty-Four Cases by Repeated Intravenous Injections of Hypertonic Salt Solution, Experience of Ten Years, *Surg, Gynec & Obst* **61** 214 (Aug) 1935

63 Herrmann, Louis G. Passive Vascular Exercises and the Conservative Management of Obliterative Arterial Diseases of the Extremities, Philadelphia, J B Lippincott Company, 1936

64 Reid, Mont R, and Herrmann, Louis G. Non-Operative Treatment of Peripheral Vascular Diseases, *Ann Surg* **102** 321 (Sept) 1935

the prevention of gangrene This, they say, has been accomplished even when sensation in the extremity was absent or markedly diminished

The value of this method of therapy, in their experience, diminishes when occlusion of the arterioles occurs unassociated with sudden increases in the pathologic process and consequently is not complicated by vasospasm Whenever the occlusive processes outbalance the ability of the collateral vessel to furnish adequate arterial blood and also upset the normal, delicately adjusted vasomotor mechanism, this form of therapy forms a most valuable adjunct In cases of thrombo-angitis obliterans the authors admit the method to be much less effective, and they think that considerable care and judgment are necessary in its use for treatment of this condition This is especially true when there is acute migratory phlebitis or when intense rest pain exists If the inflammatory process is exceedingly active pavaex therapy may do harm A spread of inflammation may result, and intense pain may follow In the quiescent phases of the disease, when the thrombo-inflammatory processes have subsided, pavaex therapy has been beneficial In patients with peripheral arterial sclerosis associated with diabetes, the arteriolar bed is usually fairly good, and pavaex therapy has been effective even in the presence of ulceration, infection and gangrene of the toes When these conditions exist it must be used with discretion, and the amounts of pressure must be varied according to the condition of the patient

Herrmann<sup>65</sup> states that the permanency of the collateral circulation developed by this method is dependent on the nature of the disturbance The increase in circulation brought about in patients with arteriosclerosis has often increased in magnitude until a definite and efficient circulatory balance has been produced In conjunction with passive vascular exercise the author has employed local artificial hyperthermia with encouraging clinical results The local application of heat increases the local metabolism of the tissues, with a consequent increased demand for arterial blood If the arterial circulation can be increased in proportion to the increase in the demand for blood, reconstructive processes should take place more rapidly The degree of local hyperthermia during passive vascular exercises should be from 104 to 106 F It is applied by supplying preheated air to the interior of the boot The use of this procedure is particularly valuable in the presence of moist, spreading gangrene in which the arteriolar pathways of the extremities are impaired

Herrmann<sup>66</sup> has shown by arteriographic studies of patients treated by passive vascular exercises an enormous increase in the size and

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65 Herrmann, Louis G The Management of Organic Peripheral Vascular Diseases, Wisconsin M J **35**:185 (March) 1936

66 Herrmann, Louis G Non-Operative Treatment of Inadequate Peripheral Distribution of Blood Passive Vascular Exercises and Local Hyperthermia, J A M A **105** 1256 (Oct 19) 1935

number of useful collateral arteries in the distal parts of an extremity which has been treated intensively. Pulsations in vessels have returned, and calorimetric and oscillometric studies have demonstrated conclusively, in his opinion, that the collateral circulation brought about by this means remains active for many months after treatment is discontinued. It is obvious that the degree to which collateral arterial circulation can be developed depends largely on the actual number of arteriolar and small arterial pathways that are open and not involved by the disease process.

The use of hyperthermia in conjunction with passive vascular exercise overcomes the peripheral vascular spasm that accompanies the active types of obliterative arterial disease and thus helps to surmount one of the most important obstacles to the formation of a sustained collateral circulation. Hyperthermia finds important application also in combination with passive vascular exercises in the treatment of arteriosclerosis obliterans with or without gangrene and with or without associated diabetes. Feet that had been subject to various degrees of freezing responded promptly, and serious sequelae were prevented in all the cases in which this method of treatment was given.

The observations of Landis and Hitzrot<sup>67</sup> on suction and pressure therapy are in essential agreement. They feel that it is a worth-while addition to other conservative methods for the treatment of peripheral vascular disease. Good results can be obtained even when organic obstruction has advanced to the stage in which the arterial blood flow can no longer be increased by methods depending on vasodilatation. They found that both the subjective and the objective phenomena of ischemia can be relieved after conservative measures have failed. They also feel that the method is of particular service in increasing the local blood flow at least temporarily, during episodes of pain or ulceration, so that time may be gained for the development of an adequate collateral circulation. They emphasize several contraindications and point out that it is necessary to investigate the extremity before each treatment, particularly when there are open lesions, to make sure that phlebitis has not developed and that infection is not spreading. A slight elevation of temperature should be an indication to proceed with extreme caution. Treatment should be discontinued in the presence of encapsulated pus. The authors conclude that therapy of this type should be applied with caution and in selected cases. They point out that the treatment should not be left in the hands of a technician but should be under the definite supervision of a physician.

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<sup>67</sup> Landis, E. M. and Hitzrot, L. H. Treatment of Peripheral Vascular Disease by Means of Suction and Pressure. *Ann Int Med* 9: 264 (Sept) 1935.

Krusen<sup>68</sup> has described a modification of the apparatus of Landis and Gibbon. It seems as if this might be somewhat more convenient for general clinical use, but fundamentally it shows no important differences. Allen and Brown,<sup>69</sup> after using the Heilmann and Reid apparatus, are much less optimistic as to the result secured. They comment on the fact that in their hands this method of treatment has not produced any results that they had not observed repeatedly following simpler methods. They feel that good results are obtained with suction and pressure management in those cases in which good results could be expected from other measures, and that when good results do not follow other measures suction and pressure treatment is usually without value. Particularly in cases of thrombo-angitis obliterans they believe the intravenous injection of typhoid vaccine is so good that this other type of treatment cannot be compared with it. According to their observations suction and pressure treatment and increases of the cutaneous temperature may relieve pain and induce the healing of ulcer. The pain of ischemic neuritis is definitely relieved. They state that the greatest therapeutic need is a satisfactory method of treating older patients with the occlusive arterial lesions of arteriosclerosis. They feel that passive vascular exercise has been of no particular help in this direction.

Conway<sup>70</sup> has reported on the use of the Heilmann and Reid apparatus. He states that in his opinion this therapeutic measure has justified its inclusion in medical therapeutics. He agrees that the method is physiologically sound, and in nine of ten cases of sudden vascular occlusion the treatment was effective. There was improvement in more than 80 per cent of the cases of arteriosclerosis obliterans, and in four cases of thrombo-angitis obliterans no benefit was derived. Conway found no evidence that this method of treatment was harmful in any case. Wilson and Roome<sup>71</sup> reported the results of twenty-three cases in which treatment was by this method. Their findings in cases of thrombo-angitis obliterans were essentially the same as those of other observers. Six of the eight patients treated showed no benefit, and two showed only slight improvement. They agree that many of the patients felt subjectively improved during the course of the treatment but

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68 Krusen, Frank Hammond. Passive Vascular Exercise for Diseases of Peripheral Vessels, *Arch Phys Therapy* **16** 581 (Oct) 1935

69 Allen, Edgar V., and Brown, George E. Intermittent Pressure and Suction in the Treatment of Chronic Occlusive Arterial Disease, *J A M A* **105** 2029 (Dec 21) 1935

70 Conway, J Herbert. Obliterative Vascular Disease. Report of Fifty-One Cases Treated With Passive Vascular Exercise, *J A M A* **106** 1153 (April 4) 1936

71 Wilson, Harwell, and Roome, Norman W. Passive Vascular Exercise. Observations on Its Value in the Treatment of Peripheral Vascular Diseases, *J A M A* **106** 1885 (May 30) 1936

reported no beneficial results when questioned two or more months later. They find it difficult to say whether the beneficial results that followed were to be attributed to this method or to the other measures concurrently employed.

Pfahler<sup>72</sup> has reported on the roentgen therapy of thrombo-angitis obliterans. He found that irradiation alone over the affected extremity did not produce satisfactory results, but with the proper doses applied over the sympathetic ganglions supplying the parts involved, he obtained excellent results. Pain was often relieved in two or three weeks, intermittent claudication disappeared and circulatory and trophic disturbances were relieved in from two to six weeks. There was an early tendency for moist gangrene to become dry, and the dead tissue gradually separated from the healed area. These results are unusually striking and seem to be important.

## SURGICAL TREATMENT A CRITICAL REVIEW

BY DR DE TAKÁTS

Contributions published since our last review can again be most conveniently grouped as dealing with (1) attempts to improve the circulation, (2) attempts to relieve pain and (3) methods of amputation.<sup>73</sup>

### VENOUS LIGATION

An explanation of the therapeutic effect of ligation of the concomitant vein in cases of arterial obstruction is attempted by Bell.<sup>74</sup> He points out the rise of venous and capillary pressure and the increase of filtration pressure over the osmotic pressure when a vein is tied. In the extremity afflicted by arterial obstruction the hydrostatic pressure in the capillaries falls below the osmotic pressure. There may be enough blood in the minute vessels, but circulation will not take place from the capillaries to the tissues, and nutrition is seriously impaired. Venous ligation restores the normal relationship between the hydrostatic and the osmotic pressure by raising the former and thus may be a temporary aid to circulation.

This principle may be successfully employed when ligation of a larger artery becomes necessary. As stated in our previous review, ligation of a concomitant vein has not been of definite benefit in cases of chronic vascular disease of the extremities.

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<sup>72</sup> Pfahler, G. E. Roentgen Therapy of Thrombo-Angitis Obliterans (Buerger's Disease), *Am J Roentgenol* **34** 770 (Dec) 1935.

<sup>73</sup> No attempt is made to offer a complete bibliography. Articles have been selected which contain new trends of thought or bring a well founded challenge to prevalent ideas, thus constituting progress in vascular surgery.

<sup>74</sup> Bell, James. The Ligation of Veins with Arteries, *Irish J M Sc*, June 1935, p 262.

## ARTERIECTOMY

The subject of arterial excision (arteriectomy) is again discussed in two papers from the clinic of Leriche. In an experimental study Fontaine and Schattner<sup>75</sup> found that the blood supply of a hindlimb of a dog is much more impaired when the thrombosed arterial segment is left in place than if an arterial segment of the same length is resected. Not only are there spasm and a slower development of collateral circulation in the presence of a thrombosed artery, but distal to the obstruction there appear endarteritis and mesarteritis or even thrombosis of the blood vessels. No such lesions are found on the arteriectedomized side. A clinical report by Leriche and Fontaine<sup>76</sup> is based on eighty cases of arterial excision. The diagnosis was syphilitic arteritis in two cases, Buerger's disease in thirty-four, arteriosclerosis in thirty-four, embolism in four and traumatic thrombosis in four cases. The femoral artery was exposed in most cases, and it was often necessary to resect segments of from 20 to 25 cm (9 to 11 inches). Arteriography with thorium dioxide was used to localize the obliterated segment. Care must be exercised not to destroy the collateral vessels close to the distal end of the obliterated artery, as they carry blood to the main vessel below the obstruction in the reverse direction.

Clute<sup>35</sup> resected short segments of the inflamed thrombosed brachial artery in two cases, partial relief was obtained in the first and complete relief in the second case. He does not believe that total removal of the involved artery is necessary, as favorable results can be obtained by simply interrupting the continuity of the artery. He makes the interesting suggestion that it may be worth-while to remove a section of the artery when ligation of a major vessel is necessary. The arterial excision, he believes, hastens the formation of collateral circulation by the interruption of the periarterial sympathetic fibers.

We have stated previously that "such an operation is not indicated in the majority of cases of peripheral vascular disease." In the occasional instance of accurately localized segmental thrombosis, such as is encountered in traumatic thrombosis, in localized arteritis and at the site of arterial ligatures, arteriectomy deserves serious consideration. The mechanism of its beneficial action lies in the interruption of afferent sensory impulses activating a sympathetic vasoconstriction through a spinal reflex and not, as Leriche thought, in paralysis of the periarterial sympathetic plexus. Reflexes originating from such occluded arterial

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75 Fontaine, R, and Schattner, R. Les bases expérimentales de l'artériectomie, *J de chir* 46 849 (Dec) 1935

76 Leriche, R, and Fontaine, R. Conditions nécessaires, résultats et technique de l'artériectomie, *Presse méd* 43 1953 (Dec 4) 1935

segments can be equally well interrupted by means of paravertebral injections of alcohol or sympathetic ganglionectomy

#### EMBOLECTOMY

In a case of acute arterial occlusion<sup>77</sup> an attempt must be made to differentiate between peripheral embolism and acute arterial thrombosis. From the probable site of the occlusion together with the patient's age and cardiovascular status one can estimate the danger of gangrene from occlusion at that particular level. Vigorous conservative measures, including the use of heat, of papaverine and of alternating suction and positive pressure, are worthy of trial. These measures serve the purpose of overcoming the concomitant vascular spasm which occurs with every sudden arterial occlusion. The probable pathways of the reflex vasoconstriction are discussed. If these conservative measures fail and if the patient is seen within the first ten hours, embolectomy is indicated. This report is based on ten cases of embolism and twenty-nine cases of acute arterial thrombosis. The author urges a less passive attitude toward peripheral vascular crises, which are still being ignored or treated with indifference.

#### PARAVERTEBRAL INJECTION OF ALCOHOL

The injection of alcohol into sympathetic nerves was used by Patterson and Stainsby<sup>78</sup> as an excellent substitute for operative procedures. The technic of paravertebral nerve block is described. It requires a thorough anatomic knowledge and many trials on cadavers. In addition to eleven patients with rheumatoid arthritis, the authors treated eight patients with Buerger's disease, and they cite the case of one patient with Raynaud's disease. The authors prefer this form of treatment to protein shock and to peripheral sensory nerve block. They have used the method for ambulatory patients.

It is true that with sufficient experience paralysis of the sympathetic innervation of an extremity can be accomplished by paravertebral injections of alcohol. It must be emphasized, however, that unless temporary results are sufficient, as in cases of acute arterial obstruction, a return of sympathetic activity may be expected. The anatomic variations of the sympathetic chain and ganglions are so great that the percentage of failures must be considerable. Finally, disturbing paresthesias and paralysis may result from injection into an intercostal or lumbar nerve. The method is valuable but requires just as much skill as the surgical exposure and excision of the sympathetic ganglions.

77 de Takats, G. Acute Arterial Occlusions of the Extremities, *Am J Surg* 33: 60 (July) 1936.

78 Patterson, R., and Stainsby, W. J. The Therapeutic Effects Following Interruption of the Sympathetic Nerves, *Ann Surg* 103: 514 (April) 1936.

## SYMPATHETIC GANGLIONECTOMY

The anatomy of the ganglionated trunk has been the subject of two exhaustive reports. Braeucker<sup>79</sup> studied the lumbosacral trunk in sixty-two cadavers and states that a number of variations exist which are accompanied with changes in the position of the lumbosacral somatic plexuses. There may be from three to six lumbar sympathetic ganglions, and differences on the two sides are frequent. He also observed that myelinated white rami may emerge from the third lumbar ganglion and also from the upper sacral ganglions—a statement contrary to current teaching. Perlow and Vehe<sup>80</sup> have given instructive diagrams of the most frequent variations of the cervicothoracic and lumbosacral chains. Not only do the size and the shape of the ganglions vary, but their relations to vessels and lymph chains and their connections to the somatic plexuses are inconstant. These investigators noted an occasional connection between the second thoracic ganglion and the first thoracic nerve. In nine of forty-eight lumbar cords dissected the lumbosacral cord divided longitudinally. Only four of the forty-eight cords presented a textbook picture of five definite ganglions with medium-sized chains. In only four of twenty-four cadavers did the cords look alike on the two sides.

These observations emphasize that a possible cause of failure following sympathectomy may be incomplete removal of the ganglionated trunk or incomplete severance of communications between sympathetic and somatic outflow. Perlow and Vehe postulate a microscopic identification of the lumbar sympathetic trunk, especially on the left side, where the trunk is surrounded by lymph vessels and glands.

A histologic study of sympathetic ganglions removed in cases of Raynaud's and Buerger's disease, acute bone atrophy and Quincke's edema is reported by Sunder-Plassmann.<sup>81</sup> He noted spotty atrophy, vacuolation, autolysis, chromatolysis in the ganglions and matting of the neurofibrils. In cases of Buerger's disease and Sudeck's atrophy there was in addition a proliferation of the intraganglionic fibrils with neuroma formation. The "mantle cells" around the ganglions were increased in number. Such ganglions send pathologic stimuli or act as multipliers of normal stimuli to the periphery, hence surgical removal is indicated.

Physiologic observations on the sympathectomized limb have added to the better understanding of the effect of this operation. Freeman<sup>82</sup>

79 Braeucker, W. Die anatomischen und physiologischen Grundlagen der lumbosakralen Sympathektomie, *Arch f klin Chir* **183** 636 (Oct 28) 1935.

80 Perlow, S., and Vehe, K. L. Gross Anatomy of the Stellate and Lumbar Sympathetic Ganglia, *Am J Surg* **30** 454 (Dec) 1935.

81 Sunder-Plassmann, P. Untersuchungsergebnisse zur Grenzstrangchirurgie, *Arch f klin Chir* **183** 653 (Oct 28) 1935.

82 Freeman, N. E. The Effect of Temperature on the Rate of Blood Flow in the Normal and Sympathectomized Limb, *Am J Physiol* **113** 384 (Oct) 1935.



showed that after sympathectomy the circulation of the hand is dependent on the metabolic requirements of the tissues. The circulatory stimulus is mediated, as first suggested by Roy and Brown in 1879, through the concentration of metabolites, perhaps their acidity. In the normal hand there is in addition a reflex control in accordance with the needs of the body, so that circulation functions as a part of the heat regulating mechanism. After sympathectomy the blood flow is no longer modified in a thermoregulatory fashion, although epinephrine will exert a strong influence.

From a practical standpoint these important observations indicate that the sympathectomized limb is more independent of thermal influences than the limb not operated on. In case of peripheral vascular disease, reflectoric vasoconstriction is thus abolished.

Other stimuli than cold, such as pain, pressure and noise, and intrinsic stimuli, for instance deep breathing, an altered temperature of the blood, visceral pain and mental activity, are all ineffective in diminishing the digital volume in the sympathectomized limb, whereas the normal reaction to all these stimuli is vasoconstriction, as measured by the diminished volume of the finger.<sup>83</sup> This vasoconstriction is independent of the integrity of the anterior and posterior roots but is dependent on the continuity of both the preganglionic and the postganglionic sympathetic fibers. It is therefore a mechanism the efferent pathway of which is a sympathetic nerve. The interruption of these fibers does not prevent an afferent stimulus from that limb from producing vasoconstriction in the digits of other limbs, but the stimulus will not produce vasoconstriction of the same limb if it is sympathectomized.

These findings seem to be of considerable importance. They mean that if an afferent painful stimulus originates in a diseased blood vessel, such as is encountered in Buerger's disease, it cannot cause reflectoric vasoconstriction in the same limb if it is deprived of its sympathetic nerve supply. These studies may throw light also on the symmetry of certain vascular lesions in cases in which a painful stimulus of one extremity causes vasoconstriction in the opposite limb.

The mechanism of the decrease in volume of the hand following a standard stimulus (a pinch) has been analyzed by Capps,<sup>2</sup> who observed it to be dependent on an increase of the tone of the veins, venules and capillaries as measured by a decrease in volume. The tone of these vessels increases with cold and decreases with heat, and excessively low or high temperatures abolish the reflex changes in volume. The reflectoric diminution in the volume of the hand can be abolished by sympathectomy.

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83 Stürup, G., Bolton, B., Williams, D. J., and Carmichael, E. A. Vasomotor Responses in Hemiplegic Patients, *Brain* 58:456 (Dec.) 1935.

Several papers have included discussions of the surgical approach to the sympathetic chain and ganglions. Flothow<sup>84</sup> has performed approximately one hundred cervicodorsal sympathectomies by the dorsal approach and is dissatisfied with the method. He advocates the anterior approach of Gask, which he has performed five times. He believes that it is possible to obtain exposure as far down as the fifth dorsal ganglion, a possibility which, on the basis of considerable experience with Gask's method, appears to me to be doubtful.

The last word in regard to the most successful approach has not been said, and we are awaiting further progress with interest. For the removal of the stellate ganglion and the dorsal chain as low as the second thoracic ganglion the anterior approach seems satisfactory. But if, as will be discussed later, the optimal sympathectomy for the upper extremity will necessitate section of the trunk below the third ganglion, the posterior muscle-splitting approach may again come into favor.

Telford<sup>85</sup> also has given up the posterior approach to the cervicothoracic ganglion after thirty-five operations because it is more mutilating, because it is followed by a more stormy convalescence and because the exposure of the stellate ganglion is unsatisfactory, as the root of the first thoracic nerve lies between the surgeon and the ganglion. He believes that failures of sympathectomy on the upper extremity may be due to an incomplete technic or the late stage of the disease but that they occur mainly because the usual cervicothoracic sympathectomy produces postganglionic degeneration of the sympathetic fibers and results in sensitization of the denervated vessels to epinephrine. The great significance of this sensitization with regard to recurrences or residual symptoms after sympathectomy has been forcibly brought out by White (see last year's review). To avoid this postganglionic degeneration, Telford cuts the sympathetic trunk below the third ganglion and cuts the second and third white rami. Smithwick and White<sup>86</sup> have developed a method of preganglionic section through a posterior approach. They cut the spinal cord below the third ganglion. In addition, the second and third intercostal nerves are resected for a length of 3 or 4 cm, as far as the intervertebral foramen, so as to interrupt all possible preganglionic rami.

Our limited experience with the preganglionic section of Telford has been most encouraging. The difference between a preganglionic and a postganglionic section is most striking in the same patient. Observations of longer duration will be necessary to determine the lasting

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84 Flothow, P. G. An Adequate Anterior Approach for the Removal of Cervicodorsal Sympathetic Ganglia, *West J Surg* **43** 589 (Oct) 1935.

85 Telford, E. D. The Technique of Sympathectomy, *Brit J Surg* **23** 448 (Oct) 1935.

86 White, J. C. Personal communication to the author.

value of this method, which represents a clinical application of the important contribution of Freeman, Smithwick and White to surgery of the sympathetic nervous system

Grant<sup>87</sup> on the basis of studies on the denervated ear of the rabbit, also comes to the conclusion that if the phenomenon of the regaining of vascular tone after sympathectomy is the same in man as it is in the rabbit, preganglionic section is preferable to ganglionectomy for peripheral vascular disease because it reduces the subsequent reactivity of the vessels. These vessels are increasingly responsive not only to epinephrine but to solution of posterior pituitary, histamine, ergotoxin, faradization and cold. The explanation of this phenomenon is left open. However, the author does not believe that the increased reactivity is due to nerve degeneration. It is apparent from one of his graphs that increased responsiveness of the vessels also develops after preganglionic section, but the vessels do not respond as vigorously as vessels of which the postganglionic fibers have been cut.

According to Woollaid,<sup>4</sup> the well known difference between results on the upper and those on the lower limb following sympathectomy is due to the increased constrictor tonus of the lower extremity developed because of the upright posture. In the light of the different responsiveness of vessels to preganglionic and postganglionic sections, however, the explanation of White seems more plausible. He pointed out that lumbar sympathectomy produces a preganglionic section for the majority of the fibers, all except those that go to the femoral and obturator nerves. Thus the degree of sensitization to epinephrine is much smaller in the lower extremity.

Several new approaches have been described for lumbar sympathectomy. Harris<sup>7</sup> advocates a transverse abdominal incision at the level of the umbilicus, cutting the oblique and transversalis muscles and the fascia of the rectus muscle but not the rectus muscle itself. This is an extraperitoneal approach, permitting the removal of one chain at a time. Rees<sup>88</sup> discusses the objections to previous methods. The posterior approach of Royle requires two operations and gives an unsatisfactory exposure of the lower lumbar ganglia. Adson's transperitoneal approach may be followed by intestinal obstruction and even fatal ileus. Flothow's<sup>89</sup> method requires a two stage operation, and the incision cannot be extended up or downward according to need. Flothow uses

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87 Grant, R. T. Further Observations on the Vessels and Nerves of the Rabbit's Ear with Special Reference to the Effects of Denervation, *Clin. Sc.* 2: 1, 1935.

88 Rees, C. F. Single Incision, Transabdominal Extraperitoneal Approach to Lumbar Ganglia, *Am. J. Surg.* 32: 234 (May) 1936.

89 Flothow, P. G. Anterior Extraperitoneal Approach to the Lumbar Sympathetic Nerves. *Am. J. Surg.* 29: 23 (July) 1935.

a muscle-splitting incision at the level of the umbilicus. Rees makes a Y-shaped incision in the midline through skin and fat and two longitudinal incisions through the fascia and the inner third of the rectus muscle. The line of cleavage between the posterior sheath of the rectus muscle and the peritoneum having been found lateral to the rectus muscle, the peritoneum is peeled medially, and the chains are exposed on both sides.

As in case of cervicodorsal sympathectomy, the choice of surgical approach is difficult, nor is it likely that one method will suit all conditions. Whether the operation is planned to be unilateral or bilateral and whether the patient is lean or obese will influence the selection of the best type of method. Surgeons actively engaged in surgical intervention on the sympathetic nervous system should be familiar with several of these methods to insure the proper selection in a given case.

Indications for and results following sympathectomy have been discussed by Harris.<sup>7</sup> Four of the seventy-five patients suffered from Raynaud's disease, and in all of them the condition was improved. Rather unusual is his group of twelve patients with peripheral arteriosclerosis, five of whom derived benefit from the operation. Of the patients with Buerger's disease, 58 per cent showed immediate and late benefit, 20 per cent of the operations having been performed too recently to make evaluation of the results possible. The immediate results were good, but amputation had to be performed later in 89 per cent, and poor results, meaning no improvement or persistence of rest pain necessitating amputation, were obtained in 12.2 per cent. The author emphasizes the fact that all the patients who showed a marked rise in the cutaneous temperature after nerve block derived benefit from sympathectomy, and sometimes even a patient with a slight rise in the surface temperature showed an appreciable increase in circulation, sufficient to turn the scale from impending gangrene to rapid healing of ulcers and restoration of the ability to undertake a limited amount of work.

Sanchís-Perpiñá<sup>90</sup> advocates sympathectomy for varicose veins, varicose ulcers and trophic ulcers. He produced trophic ulcers by injecting a 50 per cent solution of lactic acid into the lumbosacral ganglions. He leaves the second lumbar ganglion intact and thus does not abolish sweating and pilomotor reflexes. He claims to have obtained good results. It seems that this operation constitutes preganglionic sympathectomy for a large area of the lower extremity but leaves both the preganglionic and the postganglionic fibers to the femoral and obturator nerves intact and is thus an incomplete operation.

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<sup>90</sup> Sanchís-Perpiñá, V. Neue experimentelle und klinische Beiträge zur lumbosakralen Sympathikuschirurgie, Beitr. z. klin. Chir. **161**: 442, 1935.

Danielopolu and his co-workers<sup>91</sup> believe that the vasoconstrictor fibers to the hindlimbs of the dog do not pass out to the lumbar nerves or along the aortic plexus. When they stimulated the sympathetic chain above the second lumbar ganglion, they produced vasoconstriction in the hindlimbs. This effect could be almost completely abolished if the sympathetic chain had been transected at the level of the promontorium. When the distal stump of such a transected lumbosacral chain was stimulated, vasoconstriction occurred again. On the basis of these findings the authors advocate resection of the lumbosacral chain at the level of the promontorium. Clinical results on the basis of twenty-five cases have indicated to them that this relatively simple procedure, which can be performed in one stage through a midline transperitoneal approach, is just as efficacious as the much more extensive removal of the lumbar sympathetic chain from the diaphragm to the aortic bifurcation.

The method of Danielopolu obviously resembles that of Sanchís-Perpiñá<sup>90</sup> and can be again interpreted as constituting a preganglionic section of all the sympathetic fibers the cell stations of which are in the sacral ganglions. However, it leaves the fibers to the femoral and obturator nerves intact. These two nerves, with the exception of a small strip of tissue innervated by the saphenous nerve, carry no sympathetic fibers to the foot. My experience with such lumbosacral transection in persons with poliomyelitic extremities indicates that the results are not as good as those following complete lumbar sympathectomy. However, further work along these lines may be well worth while.

W. J. Merle Scott<sup>5</sup> feels that the irritation of sensory fibers around diseased or obstructed vessels is the origin for afferent impulses which cause a marked vasoconstrictor reflex. This vasoconstriction extends not only over the diseased vessel but to the anastomotic and terminal vessels on which the viability of the extremity distal to the obstruction depends. Sympathetic ganglionectomy in carefully selected cases offers the patients the most complete and permanent vasodilatation of the collateral circulation. For the severe types of angiospasm consecutive to trauma, lumbar ganglionectomy has been satisfactory.

This concept of regarding so many of the vasomotor phenomena as an efferent activation of a sensory-sympathetic reflex arc has been most fruitful in many peripheral vascular disorders. It also explains why arterial excision and sympathetic ganglionectomy are equally capable of producing vasodilatation of the collateral circulation.

Most instructive material on the results of sympathectomy performed by the Fellows of the Association of Surgeons of Great Britain and

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<sup>91</sup> Danielopolu, D., Aslan, A., and Marcou, I. La sympathectomie inter-lombosacrée dans les troubles trophiques des membres inférieurs, *J de chir* 46 657 (Nov.) 1935.

Ireland has been collected, tabulated and analyzed by J Paterson Ross<sup>92</sup> Sympathetic ganglionectomy for Raynaud's disease was carried out forty-one times. The operation when technically complete was successful in all cases of Raynaud's disease with mild involvement and in the majority of those complicated by ulceration, but when the disease was present in a severe form accompanied with scleroderma, sympathectomy was a complete failure in eight of eleven cases. The author brings out the interesting fact that scleroderma was not present in any of the patients treated by lumbar ganglionectomy and that this may be another factor in the more favorable results of lumbar as compared with cervicothoracic sympathectomy for Raynaud's disease. The results are expressed in terms of success, improvement or failure, and all patients have been followed for one year, two years or more than two years. The opinion, expressed by the author in another study<sup>93</sup> is reemphasized, i. e., the success of sympathectomy in a person with Raynaud's disease depends almost entirely on the condition of the arterial walls and by recognizing the presence of structural disease it should be possible to avoid the disappointment which follows a faultless operation performed in an unsuitable case. My own experience with Raynaud's disease in its different stages is entirely in accord with this statement regarding the structural element as one of the causes of failure.

The tabulated results of lumbar ganglionectomy in sixty-six cases of thrombo-angitis obliterans confirms the prevalent impression that intermittent claudication is a symptom which is difficult to relieve. Rest pain, however, and gangrene in an early stage often respond favorably to ganglionectomy. The study of these cases has failed to indicate any clinical picture by which one can forecast the result of the operation. The response of the cutaneous temperature to spinal anesthesia is sometimes helpful, but a poor response must not be regarded as a clear contraindication to ganglionectomy. It is questionable whether the pathologic process can be retarded by the operation. Popliteal thrombosis may develop after the operation and necessitate amputation. Cervicothoracic ganglionectomy was performed in three cases, the operation being successful in two cases but a complete failure in the third case.

The proper selection of patients suffering from Buerger's disease for sympathetic ganglionectomy is still an open question. In my experience remarkable benefit lasting over several years may be obtained, but the preoperative and postoperative conservative treatment must be just as

92 Ross, J Paterson. The Results of Sympathectomy. An Analysis of the Cases Reported by Fellows of the Association of Surgeons, Brit J Surg **23** 433 (Oct) 1935.

93 Ross, Paterson J. The Recognition of Structural Changes in the Arteries in Raynaud's Disease, St Barth Hosp Rep **68** 121, 1935.

meticulous as if the operation had not been undertaken at all. Analogy with the results of the surgical treatment of duodenal ulcer readily suggests itself.

Twenty-six patients with impairment of the circulation in the legs following infantile paralysis were treated by lumbar ganglionectomy and one patient was treated by cervicothoracic ganglionectomy. In a group of nine cases in which the affected limb was merely cold and cyanosed, the operation was eminently successful, both the color and the temperature of the affected limb being restored to normal. In a group of seventeen cases in which there was ulceration, thirteen legs were successfully treated and two were improved and in two instances the operation was a failure (with persistent ulceration in one case and pain necessitating amputation in the other). One case was reported in which lumbar ganglionectomy had been performed for "trophic" ulceration of the leg accompanying spina bifida. The operation was unsuccessful.

Lumbar ganglionectomy was performed in fourteen cases for "erythrocyanosis frigida." This condition, which is described by the author as showing characteristic patches of mottled red and blue discoloration, thickening of the tissues and occasional ulceration, affects the legs of young women. The reports are satisfactory, but in my clinic such a condition is usually regarded as being on an endocrine basis, and at least a trial with active endocrine preparations is attempted. The hard edema does not subside after sympathectomy, the limb seldom recovers its natural shape.

In nine cases of causalgia sympathectomy afforded remarkable relief from pain. Sympathectomy was undertaken only after the pain had persisted in spite of the removal of any local stimulus. The most suitable cases of sympathectomy seemed to be those in which the pain was accompanied with vasomotor phenomena such as cyanosis and flushing of the skin, oversensitivity to changes in temperature and an excessive secretion of sweat. Any gross cause of local nerve irritation should be removed previously.

In the conclusion of this most significant analysis, Ross states that sympathectomy is undertaken not for the purpose of excising diseased structures but for the purpose of rectifying functional disorders in an organ the activity of which is controlled by sympathetic impulses. If Sunder-Plassmann's<sup>91</sup> histologic observations are confirmed by others at least in some instances diseased or irritated ganglions are being removed by these operations.

Harris and MacDonald<sup>94</sup> have continued their study on the rate of growth of a paralyzed poliomyelitic extremity after sympathectomy.

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94 Harris, R. I., and MacDonald, J. L. Effect of Lumbar Sympathectomy on Growth of Legs Paralyzed by Anterior Poliomyelitis, *J. Bone & Joint Surg.* 18: 35 (Jan.) 1936.

They state that a prolonged increase in the blood supply of a growing child can result in acceleration of the growth of the extremity. Thus they noted an increased rate of growth in a child following removal of the left lumbar sympathetic chain for Hirschsprung's disease. Even in poliomyelitic limbs the rate of growth can be accelerated. The shortness which follows paralysis of the lower extremity is due to the loss of accessory factors which normally enhance the basic rate of growth from the epiphyseal line such as contractions of the normal musculature and the maintenance of a normal blood supply. The factors which favor a good result are (1) paralysis limited to one extremity, (2) a moderate degree of paralysis and (3) an early operation, preferably at the age of 6 years or less, which results in a persistent increase in the circulation. This is obtained by ganglionectomy but not by laminection.

Valdoni<sup>95</sup> reports on two patients suffering from Raynaud's disease in whom cervicothoracic sympathectomy resulted in complete failure but finally the administration of filtered urine of pregnant women diminished the number and intensity of the attacks. In analyzing the two cases it becomes apparent that (1) both patients were in the third stage of Raynaud's disease and (2) in both cases the operation was postganglionic section of fibers to the upper extremity, which is known to give rise to recurrences frequently.

#### AMPUTATION

Major and minor amputations still play an important part in the surgical treatment of peripheral vascular disease. McKittrick<sup>96</sup> published interesting figures on the percentage of amputations for thrombo-angitis obliterans, arteriosclerosis and diabetes. Of fifty-three patients with thrombo-angitis obliterans, 32 per cent had a minor and 26.4 per cent had a major amputation, only three being subjected to sympathetic ganglionectomy. Of fifty-five arteriosclerotic patients, 9.1 per cent had a minor and 54.5 per cent needed a major amputation. In the group of two hundred and fifty-three diabetic patients 2.7 per cent had a minor and 46.3 per cent had a major amputation. The per cental decrease of minor and the increase of major amputations from the first group to the third group is illuminating. The author's radical surgical approach in cases of Buerger's disease is in contrast to the statement of Samuels,<sup>61</sup> who never has to amputate in cases of Buerger's disease except to remove massive gangrene. In cases of progressive extension of gangrene with rapidly spreading infection and destruction of much weight-bearing tissue an early, high amputation is advocated by McKittrick,

95 Valdoni, P. Osservazioni cliniche in due casi di morbo di Raynaud recidivati a operazioni sul simpatico, Policlinico (sez. chir.) **43** 32 (Jan.) 1936.

96 McKittrick, L. S. Indications for Amputation in Progressive Arterial Obliteration of the Lower Extremities, *Ann. Surg.* **102** 342 (Sept.) 1935.



preferably the Gritti-Stokes procedure. The mortality following amputation can be steadily decreased, it was around 15 per cent in this series. The basic unavoidable mortality following amputation in such a group is 5 per cent.

With newer technical procedures such as those of Beverly Smith<sup>97</sup> and Callander<sup>98</sup> the danger of shock, the exposure of large surfaces of muscle and the opening of numerous fascial planes inviting ascending infection have been minimized. Amputation is becoming a delicate operation requiring clean anatomic dissection, avoidance of unnecessary trauma and the giving of due consideration to proper weight bearing and painless, freely movable scars. A patient with a well fitted, suitable artificial limb may well be of higher economic efficiency than a patient whose leg has been "saved" but who is a bedridden and painridden invalid, never sure of freedom from future danger. The internist who submits a patient at the terminal stage of a vascular disease for operation and the surgeon who recognizes no conservative measures for the treatment of peripheral vascular disease should give way to a closely cooperating unit of men actively engaged in the treatment of peripheral vascular disease. Improvement in statistics invariably follows such group study.

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97 Smith, Beverly C. Amputation Through Lower Third of Leg for Diabetic and Arteriosclerotic Gangrene, *Arch Surg* **27** 267 (Aug) 1933

98 Callander, C L. A New Amputation in the Lower Third of the Thigh. *J A M A* **105** 1746 (Nov 30) 1935

## News and Comment

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The Sixth Annual Convention of the Biological Photographic Association will be held in Boston (Hotel Lenox) from September 24 to 26. An invitation is extended to scientists to attend. There will be an exhibition of photographs from all over the country and of the most modern equipment and supplies.

Active membership is open to those whose duties include biologic photography. Any one who is interested in such photography may become an associate member. The annual dues, including a subscription to the journal, are \$3.00. Further information may be procured from the secretary, Miss Anne Shiras, the Magee Hospital, the University of Pittsburgh, Pittsburgh.

The following papers are included on the program: "Ultra Slow Mercuric 'Spark' Motion Picture Apparatus," by Dr. H. E. Edgerton, of the Massachusetts Institute of Technology, Boston; "Print Quality," by Ralph P. Creer, of the Veterans Administration, Hines, Ill.; "Infra-Red Photography," by Leo C. Massopust, of the Research Laboratory of the Marquette University School of Medicine, Milwaukee; a paper on optics, the title to be announced, by Prof. A. C. Hardy, of the Massachusetts Institute of Technology, Boston; "Orthostereoscopic Photography," by Mr. Henry F. Kurtz, of the Scientific Bureau, Bausch & Lomb Optical Company, Rochester, N. Y.; "Motion Pictures as an Aid in Teaching Entomology," by Dr. C. T. Brues, of the Department of Biology, Harvard University, Cambridge, Mass.; and "Experimental Motion Pictures of the Larynx," by Leonard Juhn, of the Mayo Clinic, Rochester, Minn.

The association publishes a quarterly journal. It circulates its print exhibition as a traveling salon, and it has a series of instructive illustrated albums for the use of its members.

## Book Reviews

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**Thérapeutique hydro-climatologique des maladies du foie et des voies biliaires** By Paul Carnot, Maurice Villaret and Rene Cachera Paper Price, 20 francs Pp 152 Paris Masson & Cie, 1935

The tone of this tract is set at the start when it is remarked that the chief benefit from hydrotherapy lies in the realm of the mild functional insufficiencies of the liver that cannot be detected by laboratory tests. The discussion of the indications for this form of therapy proceeds from this point. In general, it seems that in the "pre-" states, such as *l'état pré-lithiasique* and *l'état pré-cirrhotique*, the condition is most amenable to hydrotherapy, while this form of treatment is contraindicated in cases of frank cirrhosis, lithiasis and cholecystitis. An exception is made in the case of mild hepatitis. The diagnosis of these conditions that may improve with hydrotherapy is too generalized to be of value.

The section devoted to an explanation of the "cure" is vague. The data reported impresses one by the lack of controlled experiments. Throughout this section generalities relating to the acid-base equilibrium,  $pH$ , choleresis, glyco-regulation, antianaphylaxis and cholesteremia follow one another indiscriminately in profusion. There are no chemical data of any kind listed to illustrate the benefit of the "cures." The section on climatology and disease of the liver is regrettably brief, one is curious to know why an elevation of from 600 to 1,000 meters has a sedative and regulative action on the neurovegetative equilibrium, especially in persons with vagotonia.

The final section is devoted to an illuminating description of the characteristics of the water and the therapeutic benefits of various resorts. It is interesting to note that the largest mineral content of the drinking spas is about 8 Gm of sodium bicarbonate per liter, and the daily consumption seldom exceeds 2 liters. The authors admit that there are springs elsewhere as good as those in France. The whole volume has a resemblance to a catalog of proprietary remedies.

**Das Ventrikologram** By Erik Lysholm, assisted by Bertil Ebenius and Hans Sahlstedt, of the Röntgeninstitut, Serafimerkrankenhaus, Stockholm Part I Röntgentechnik Acta Radiologica, Supplementum XXIV, 1935

This valuable work of some seventy-five pages is a definite contribution to ventriculography. The authors have had at their disposal the material of Professor Olivecrona and Professor Antoni at Serafimerlasarettet in Stockholm. During the past ten years they have studied almost 2,000 patients pneumographically and 112 by the use of iodized oil. Of the total number, 340 were considered to be normal and form the material of this well illustrated report, which gives in detail the technic used in this important clinic.

The authors state "In addition to the more conventional projections, many special methods were developed for the study of the various parts of the ventricular system. Thus, routine roentgenography was gradually supplanted by a technic which individualized each case." Variations in the amount of air injected, the position of the subject's head and the angle of projection brought out with considerable clearness the particular parts of the ventricular system under suspicion. Twelve such combinations are described and are illustrated with reproductions of the roentgenogram obtained in each case. In ten of the twelve methods the patient is placed in the horizontal position either prone or supine, and the neck is flexed or extended in order to bring different portions of the ventricular system uppermost. Sagittal, half-apical and lateral projections are utilized. Lateral and sagittal projections taken with the patient in the upright position are also utilized.

The results obtained for the normal subject are convincing. A degree of detail has been achieved which is often impossible to obtain with other methods, and the flexibility of the technic allows the concentration of attention on the suspected areas. The half-axial projections seem particularly revealing. One awaits with interest the publication of the results obtained by these methods in the study of pathologic material.

**Russell A Hibbs Pioneer in Orthopedic Surgery, 1869-1932** By Dr George M Goodwin Price, \$2 Pp 136 with 15 illustrations and 2 diagrams New York Columbia University Press, 1935

So often even the best type of doctor lives his life, does what he can to be useful, dies and is soon forgotten, except for a more or less perfunctory death notice, that it is a comfort to read a sympathetic medical biography written by a man's friends.

The author of this book has painted a pleasant portrait of Dr Hibbs—a fine doctor, a tall, rangy, upstanding, colorful, ingenious Kentuckian who came to New York as a youngster, fought his way unaided to the front ranks of American orthopedic surgery and eventually became professor of orthopedic surgery at Columbia University. During his lifetime he made many friends, vastly enjoyed being alive and contributed definitely to the advancement of his specialty.

His story is told briefly by Dr Goodwin. Dr Karl Vogel's tribute, which appeared originally in the *New York Times* is reprinted. Dr Samuel W Lambert has written a delightful chapter on Dr Hibbs as a sportsman—an interesting characteristic to emphasize, for so often in thinking of a doctor one forgets that affectionateness, humor and skill in the art of friendship do more to keep memories alive than does professional ability.

The remainder of the book is comprised of Dr Hibbs' four most significant contributions to orthopedic surgery, entitled "Lengthening the Tendo Achillis" (1900), "An Operation for Stiffening the Knee Joint" (1911), "An Operation for Progressive Spinal Deformities" (1911) and "A Preliminary Report of Twenty Cases of Hip Joint Tuberculosis Treated by an Operation Devised to Eliminate Motion by Fusing the Joint" (1926).

Those who knew Dr Hibbs will be glad to own this little volume, and others will be glad of an opportunity to become acquainted, even vicariously, with so staunch a character.

**Studies on Bone Marrow from Sternal Puncture** By Nils Goran Nordenson From the IV Medical Service, St Erik's Hospital, Stockholm, Sweden Pp 204, with 8 colored plates Stockholm Bortzells, Esselte, 1935

As the foreign literature is becoming replete with articles concerning the examination of bone marrow aspirated from the sternum for biopsy, a comprehensive review of the subject in English is welcome. This lengthy monograph, covering the literature to the time of its publication (368 items in the bibliography) and incorporating the author's observations made in over three hundred biopsies, falls short of excellency. Its very completeness encumbers its clarity. The hematologist will discover material of definite value but will find the reading laborious. In addition to the twenty-one errata listed, there are many typographic errors. It is difficult to correlate the author's data, as the case protocols and the tables of data on the peripheral blood and on the bone marrow are grouped separately, also, the patients are referred to in the tables by number rather than by diagnosis. The complexity of hematologic nomenclature is allowed to "run riot," although the author describes carefully each type of blood cell used in his differential counts. The selection of normal patients (sex not indicated) may be criticized, as fourteen of thirty-nine patients had red blood cell counts below 4,500,000, and only six had counts above 5,000,000. The hemoglobin values should

be given in grams per hundred cubic centimeters rather than in percentages. All cases of anemia in which a specific diagnosis of pernicious anemia was not made are classed as cases of secondary anemia, so this group includes an extremely heterogeneous collection. The colored plates are excellent. In spite of the many faults in presentation, this work is a valuable contribution to hematology.

**Initiation à la pathologie digestive** By P. Harvier. Price, 22 francs. Pp. 162. Paris: Masson & Cie, 1935.

This book is intended primarily for the medical student as an introduction to clinical gastro-enterology, but it merits the attention of his instructor as well. The transference of the student's preclinical knowledge from the laboratory to the patient requires a simple, concise yet thorough presentation. The author never loses sight of this objective.

Disturbances of the digestive tract are treated in the light of alterations of the gastro-intestinal physiology. Without minimizing the physiologic solidarity of the digestive functions, the author has divided his text into a consideration of motor, sensory and secretory disturbances. Particular stress has been placed on the importance of the patient's history, although physical and laboratory findings are adequately considered. Roentgenologic findings are described, typical films being shown, and are considered a definite aid to the student in completing his mental picture of the clinical features of certain conditions.

Some of the author's statements are necessarily dogmatic. The discussion of the physiology of the digestive juices is incomplete, and the almost entire disregard of pathologic conditions of the liver, gallbladder and bile-duct seems inadvisable. Open to grave criticism is the unqualified suggestion that a preparation of barium be given by mouth as an aid in the diagnosis of intestinal obstruction. However, the author has handled a difficult assignment in a most efficient manner.

**Infant Nutrition** By W. McKim Marriott, M.D., Professor of Pediatrics, Washington University School of Medicine. Second edition. Price, \$4.50. Pp. 431, with 27 illustrations. St. Louis: C. V. Mosby Company, 1935.

The first edition of this book appeared in 1930 and was received kindly. Every one knew the abilities of the author and felt sure that any volume on infant nutrition from his pen would be worth reading. Therefore the reviews, on the whole, were favorable. *The Journal of the American Medical Association* (95:1448 [Nov. 8] 1930) stated "in the brief period since it was first made available, the book has received an extraordinary popularity."

There were certain faults in the book, generally admitted, the most serious being its typography. The size and shape were wrong, the paper was rough rather than smooth so that the printing appeared to be indented rather than standing out, and, on the whole, anatomically, there were several undesirable features. All these have been eradicated.

The second edition of "Infant Nutrition" is better printed and of far more attractive appearance than its predecessor. It has been revised, added to and subtracted from for the sake of improvement. It fully deserves the popularity and praise which no doubt it will again acquire.

**Beiträge zur Pathogenese und Epidemiologie der Infektionskrankheiten** By Prof. Dr. med. H. A. Gins. Price, 5.50 marks. Pp. 127, with 6 illustrations. Leipzig: Georg Thieme, 1935.

A brief summary of some of the fundamentals of infection and immunity is given for the benefit of the general practitioner or student not specially conversant with the subject. The exposition is clear and simple and makes a continuous story, not interrupted by too many references to the literature.

## EXERCISE IN DIABETES MELLITUS

ALEXANDER MARBLE, M D

AND

RACHEL M SMITH, A B

BOSTON

Exercise along with diet and insulin is an accepted part of the present day treatment of diabetes<sup>1</sup> Its ability to increase the blood sugar-lowering effect of insulin is well recognized<sup>2</sup> Under certain conditions, however, exercise may cause a marked *increase* in the sugar content of the blood of a diabetic subject This occurs particularly if the diabetic condition is severe and if several hours have elapsed since insulin and food were given Such a finding is in keeping with the clinical observation of the preinsulin days that, whereas patients with mild diabetes profited by exercise, those with severe diabetes were often unable to tolerate it<sup>3</sup>

In this connection the studies of Grote,<sup>4</sup> Burger and Kramer<sup>5</sup> and Richardson<sup>6</sup> are of especial interest Richardson found that the effect

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From the George F Baker Clinic, Elliott P Joslin, M D, Medical Director, the New England Deaconess Hospital

Aided by the Chemical Foundation and the Proctor Fund (of Harvard University) for the Study of Chronic Disease

1 Joslin, E P, Root, H F, White, P, and Marble, A The Treatment of Diabetes Mellitus, ed 5, Philadelphia, Lea & Febiger, 1935, pp 299-301

2 Lawrence, R D The Effect of Exercise on Insulin Action in Diabetes, Brit M J **1** 648 (April 10) 1926 Gerl, A, and Hofmann, A Muskularbeit und Insulinbedarf beim Diabetes, Klin Wchnschr **7** 59 (Jan 8) 1928

3 Allen, F M, Stillman, E, and Fitz, R Total Dietary Regulation in the Treatment of Diabetes, Monograph 11, Rockefeller Institute for Medical Research, 1919, p 468 von Noorden, C H, and Isaac, S Die Zuckerkrankheit und ihre Behandlung, ed 8, Berlin, Julius Springer, 1927, pp 133-136 Lichtwitz, L Ueber den Einfluss der Muskularbeit auf den Gehalt des Blutes an Zucker und Milchsäure, Berl klin Wchnschr **51** 1018 (June 1) 1914 Kulz, E, and Rumpf, T Klinische Erfahrungen über Diabetes mellitus, Jena, Gustav Fischer, 1899

4 Grote, L R Ueber die Beziehungen der Muskularbeit zum Blutzucker, Halle, Carl Marhold, 1918

(Footnotes continued on next page)

of exercise on the diabetic patient depended on the initial level of the blood sugar. In patients who had been given neither food nor insulin for sixteen hours exercise caused a decrease in the blood sugar content when the initial value was below 175 mg per hundred cubic centimeters and an increase when the initial value was above 300 mg per hundred cubic centimeters.

#### METHODS

Young diabetic patients in good physical condition were chosen for the tests. Except when otherwise stated, all the studies here reported were carried out in the early morning after an overnight fast of from twelve to fourteen hours. All injections of insulin were made subcutaneously.

Exercise of three types was employed: running at a definite rate, working on a rowing machine and stair climbing. Since we were not interested in closely comparing patient with patient and since the amount of work in each case had to be governed by the ability of the patient to perform it, no standardized amount of exercise was adopted. Every care was taken, however, to secure adequate control curves, and to ascertain under various conditions the effect of a given amount of work on each patient. Exercise was never carried to the point of undue fatigue.

Capillary blood obtained by puncture of the lobe of the ear or of a finger was used for the determinations of sugar. Samples were collected before each test was started and at frequent intervals throughout the test, which lasted usually for from one to two hours. Sugar was determined according to the micromethod of Folin.<sup>7</sup>

#### RESULTS

**CASE 1**—Mr. N. C., 27 years of age, with severe diabetes of six years' duration, was admitted to the New England Deaconess Hospital with extensive cellulitis of the face and neck. Improvement was slow because of persistent infection of the skin and subcutaneous tissues and recurrent superficial abscesses. Eleven months later, when the patient was up and about and was ready for discharge, exercise studies were carried out. With a diet of 211 Gm of carbohydrate, 94 Gm of protein and 100 Gm of fat daily and with the use of from 56 to 60 units of insulin a day, the diabetic condition was under good control.

Chart 1 shows the effect of exercising on a rowing machine on the blood sugar levels of this patient. The solid black blocks represent periods of exercise, and their length is indicative of the duration of the activity. Between the periods of exercise the patient lay or sat quietly. Curves *A* and *B* are particularly to be contrasted. The former shows the striking rise in the blood sugar content which followed exercise without insulin (the patient had had no insulin since 2 units was given at midnight). Curve *B* shows the equally striking fall obtained when 8 units of insulin was given at 5:30 a.m., ninety-eight minutes before the exercise was begun. Curves *C* and *D* are control curves and represent the behavior of the

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5 Burger, M., and Kramer, H. Ueber die durch Muskelarbeit hervorgerufene Steigerung der Insulinwirkung auf den Blutzuckergehalt beim normalen und gestorten Kohlehydratstoffwechsel und ihre praktische und theoretische Bedeutung, *Klin. Wchnschr.* 7:745 (April 15) 1928.

6 Richardson, R. Factors Determining the Effect of Exercise on Blood Sugar in the Diabetic, *J. Clin. Investigation* 13:699 (July) 1934.

7 Folin, O., and Malmros, H. An Improved Form of Folin's Micro Method for Blood Sugar Determinations, *J. Biol. Chem.* 83:115 (July) 1929.

blood sugar level without and with insulin, respectively, with the subject at rest (lying in bed) In the case of Curve D, 8 units of insulin was given at 5 30 a m, sixty-eight minutes before the first blood sugar value was recorded In themselves curves C and D are interesting, for they demonstrate well the morning rise of the blood sugar level which may occur in a patient with severe diabetes and the effect on this of a relatively small dose of insulin

It was thought desirable to determine the effect of another type of exercise Accordingly, serial determinations of blood sugar were made before and after

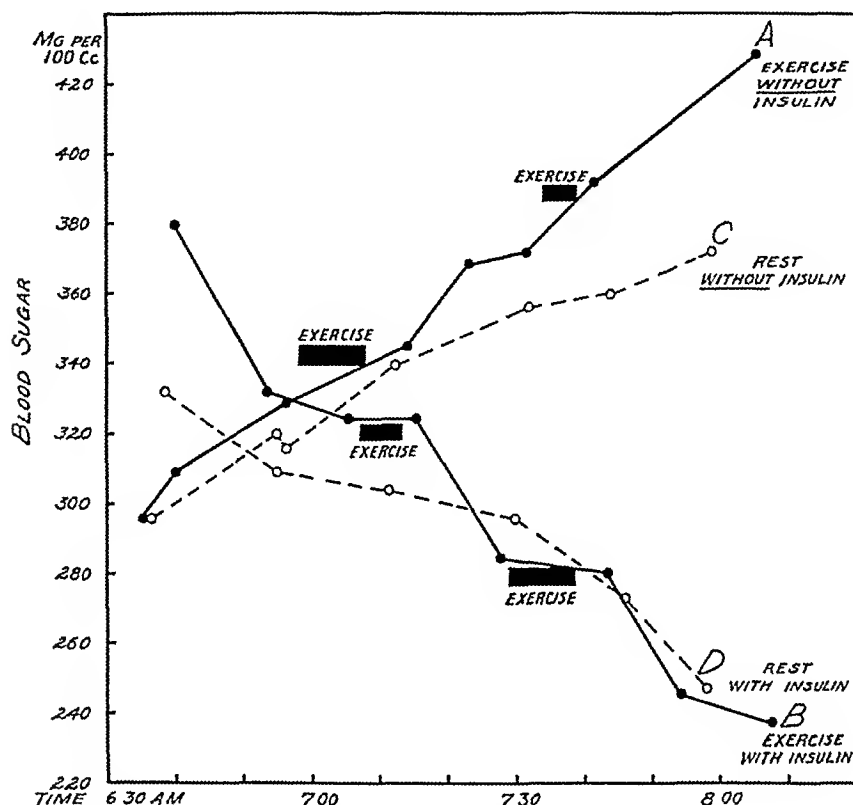


Chart 1 (case 1, Mr N C)—Curve A No insulin had been given since the midnight dose of 2 units, six and one-half hours prior to the exercise test on June 9 The first period consisted of rowing on a machine at a moderate rate, twenty-two strokes per minute, for ten minutes The second period consisted of more active rowing, twenty-eight strokes per minute, for five minutes Curve B Eight units of insulin was given at 5 30 a m on June 14 The first period of exercise consisted of mild activity, twenty-one strokes per minute on a rowing machine, for five minutes The second period consisted of moderate activity, twenty-seven or twenty-eight strokes per minute, for ten minutes Curve C No insulin had been given since the midnight dose of 2 units, six and one-half hours before the experimental period was begun on June 10, the patient resting during that period Curve D Eight units of insulin was given at 5 30 a m on June 13, the subject being at rest throughout the period noted It will be seen from curve A of this and certain of the other charts that there was a slight rise in the blood sugar content before the exercise was begun We attribute this to the fact that usually after one or two control samples of blood had been secured with the patient in bed, he was allowed to get up, dress partly and walk a short distance to the place where the studies were to be carried out Before the exercise was actually begun an additional control sample was taken This sample, probably because of the small amount of activity which had been permitted, at times had a slightly higher sugar content than the samples taken before the patient had stirred from bed



this patient had walked or run for short periods. The studies were carried out with the patient in the fasting state. No food had been given since the evening meal of the previous day, and no insulin had been administered since the dose of 2 units at midnight. The rise in the blood sugar content was striking, as is evident from table 1.

CASE 2—G D, a 138 year old boy, who had had diabetes since the age of 47 years, was in good physical condition at the time the exercise tests were made. With a diet containing carbohydrate, 170 Gm, protein, 84 Gm, and fat, 86 Gm, and with the use of from 34 to 40 units of insulin a day, the diabetic condition was under fairly good control.

Chart 2 shows the effect of exercise on the blood sugar content. Curve A demonstrates the rise obtained (from 300 to 396 mg per hundred cubic centimeters in seventy-five minutes) when the patient had had no insulin since the dose of 2 units at 10 p m the preceding day. Unfortunately the control curve B starts at a considerably higher level, but in its extent it shows relatively little tendency to rise.

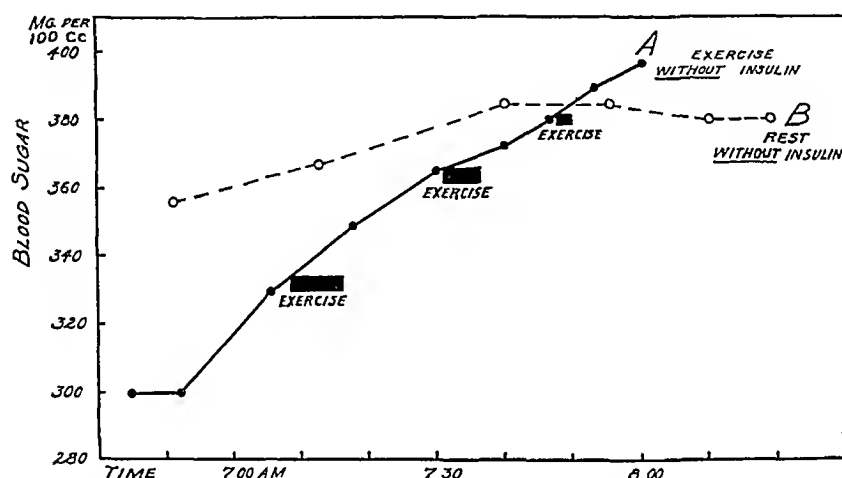


Chart 2 (case 2, G D)—Curve A. No insulin had been given since a dose of 2 units at 10 p m, eight and three-fourth hours before the exercise was begun on March 29. The first two periods of exercise consisted of rowing on a machine at a moderate rate for eight and six minutes, respectively. The third period consisted of running at low speed (a "dog trot") for two minutes. Curve B. No insulin had been given since a dose of 2 units at 10 p m, eight and three-fourths hours before the experimental period on March 28, the subject resting during that period.

TABLE 1—Data on the Effect of Exercise on the Blood Sugar Content\*

Time, a m	Blood Sugar, Mg per 100 Cc	Comments
6 53	480	Patient in bed
7 06	488	Patient in bed
7 15-7 22		Walking at approximately 4 miles per hour
7 27	496	
7 36	524	
7 40-7 45		Running at moderate rate with short final spurt of 30 seconds
7 49	532	
8 10	564	
8 19	564	

\* Mr N C, case 1, had received no insulin for seven hours prior to exercise on June 24

The results of other control studies which were carried out with this patient may be summarized as follows

**Exercise with insulin on March 30** The patient was given 5 units of insulin subcutaneously at 5 30 a m The last previous dose of insulin was 4 units at 10 p m the preceding day The blood sugar value at 6 50 a m was 192 mg per hundred cubic centimeters After two separated periods of exercise on the rowing machine (for six and five minutes, respectively) and running at a brisk "dog trot" for three minutes, the blood sugar value was 150 mg at 7 24 a m, 128 mg at 7 46 a m and 114 mg at 8 02 a m

**Rest with insulin on March 31** The patient was given 5 units of insulin subcutaneously at 5 30 a m The last previous dose of insulin was 4 units at 10 p m the preceding day The blood sugar value at 6 47 a m was 246 mg per hundred cubic centimeters The patient rested in bed throughout the study period while

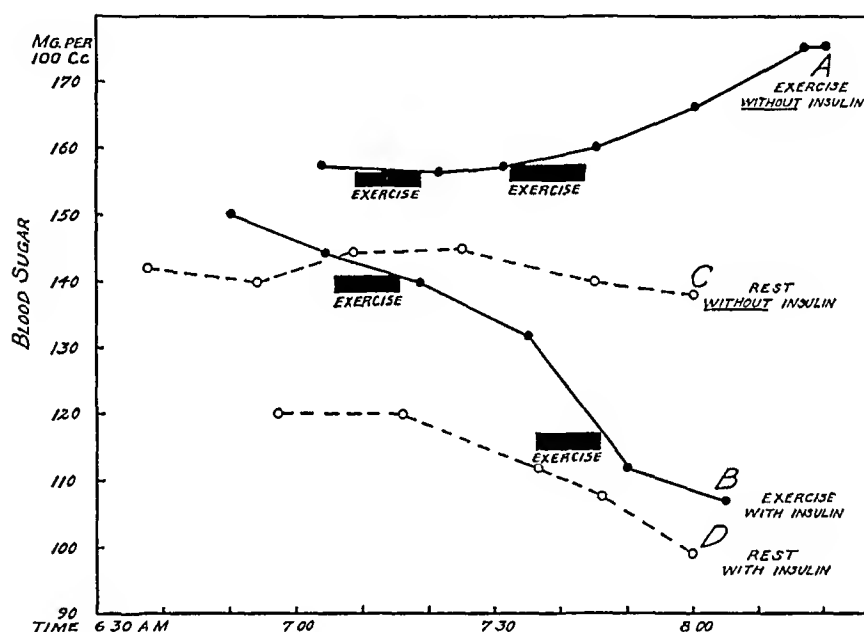


Chart 3 (case 3, Mr C H) —Curve A On May 15 no insulin had been received for over twelve hours before the experimental period The two periods of exercise consisted of rowing a machine at a moderate speed for ten and eleven minutes, respectively Curve B On May 11 the conditions were the same as for curve B except that at 6 53 a m 8 units of insulin was given Curve C On May 9 no insulin had been given for over twelve hours, and the patient was at rest in bed during the experimental period Curve D On May 12 the conditions were the same as for curve C except that at 6 58 a m 8 units of insulin was given

determinations of blood sugar were made at intervals The blood sugar value was 172 mg at 7 25 a m, 144 mg at 7 52 a m and 137 mg at 8 01 a m

**CASE 3—Mr C H**, 30 years of age, had had diabetes for four months He was in good general health when the exercise tests were carried out With a diet containing carbohydrate, 173 Gm, protein, 80 Gm, and fat, 116 Gm, and with the use of from 22 to 30 units of insulin a day the diabetic condition was under good control

Chart 3 shows again in curve A the rise in the blood sugar content which follows exercise when no insulin has been given previously The exercise in this

instance consisted of the use of the rowing machine at a moderate rate for two periods of ten and eleven minutes, respectively. The last dose of insulin had been given at about 6 p. m. the preceding day.

Curve *B* shows the characteristic fall produced by exercise (on the rowing machine) when insulin has been given shortly before. In this instance the patient received 8 units of insulin at 6:53 a. m. Curve *C* is a control curve. Without insulin or food the blood sugar content with the patient at rest remained practically constant. This contrasts with the corresponding curve in chart 1, the difference undoubtedly being due to the fact that the diabetic condition in case 1 was much more severe than that in case 3. Curve *D* shows the fall in the blood sugar content which took place with the patient at rest when 8 units of insulin was given at 6:58 a. m.

In addition to these tests, the effect of running at moderate speed (over a mile in ten minutes) was determined. In table 2 are listed the findings. The subject was in the fasting state and had had no insulin for thirteen hours. That a definite rise in the blood sugar level was obtained is shown in table 2.

TABLE 2—*Data on the Effect of Exercise on the Blood Sugar Content\**

Time, a. m.	Blood Sugar, Mg. per 100 Cc.	Comments
7:07	169	Resting in bed
7:10	174	Resting in bed
7:15-7:25		Running at rate of 6 or 7 miles per hour
7:28	185	
7:28-7:52		Mild activity about room
7:52	194	
8:10	213	Resting in bed
8:23	216	Resting in bed

\* Mr. C. H., case 3, had received no insulin for thirteen hours prior to the test on May 18.

Because of the results obtained in the early morning, the patient was naturally interested to know how exercise in the late afternoon would affect the blood sugar content, particularly since no insulin was taken before the noon meal. Accordingly, on two successive days he was allowed to take two short periods of exercise (rapid walking or running) about three hours after lunch. The results are shown in table 3.

On each occasion the exercise caused a marked lowering of the blood sugar content. This definite effect was surprising in view of the fact that the patient had received no insulin for eight hours.

In going over Richardson's <sup>6</sup> results we note that he obtained similar results in two cases. By omitting the morning insulin entirely and repeating the test he obtained the same result and so assumed that the "intake of food provided a condition which, with exercise, resulted in reduction of blood sugar." It is possible that the effect of food has been to increase the amount of effective endogenous insulin. This conclusion is strengthened by the findings of Burger and Kramer <sup>5</sup> and of

Strandell,<sup>8</sup> although Hetzel and Long<sup>9</sup> from not entirely comparable experiments reported that in the diabetic patient the reduction by exercise of postcibal hyperglycemia occurred only when insulin had been recently administered

CASE 4—R A, a 131 year old boy, had had diabetes for six and seven-tenths years With a diet of carbohydrate, 281 Gm, protein, 99 Gm, and fat, 55 Gm, allowing 2,015 calories per day and with 56 units of insulin a day, the diabetic condition was under good control The physical condition was fairly good, and examination showed no abnormalities except enlargement of the liver

Chart 4 shows strikingly the elevation of the blood sugar content caused by two periods of stair climbing of five minutes each with the patient in the fasting

TABLE 3—*Data on the Effect of Exercise in the Late Afternoon on the Blood Sugar Content<sup>1</sup>*

Time, p m	Blood Sugar, Mg per 100 Ce	Comments
May 31, 3 39	224	
3 51	225	
4 05	220	
4 10 4 20		Walking briskly $\frac{3}{4}$ mile
4 28	193	
4 30 4 38		Running $\frac{3}{4}$ mile
4 42	187	
5 20	164	
5 30	163	
June 1, 4 29	188	
4 32	190	
4 45	182	
4 56	175	
4 57 5 07		Walking briskly $\frac{3}{4}$ mile
5 10	164	
5 11 5 16		Running $\frac{3}{4}$ mile
5 20	160	
5 35	144	
5 54	132	
6 15	124	
6 21	112	

\* Mr C H, case 3, on May 31 had a last dose of 16 units of insulin at 7 20 a m He took a normal amount of exercise during the day and had lunch at 12 45 p m On June 1 he had a last dose of 14 units of insulin at 7 40 a m He took a moderate amount of activity during the day and had lunch at 12 45 p m

state He had had no insulin since 10 p m (4 units) the previous evening In five minutes he was able to go twice up and down ninety-eight steps, each 185 cm high He was only mildly fatigued at the end of the period of exercise The body weight was 77 $\frac{3}{4}$  pounds (35.3 Kg)

Curve B is a control curve showing the behavior of the blood sugar content with the patient at rest throughout the experiment (no insulin since 4 units at 10 p m the previous evening)

8 Strandell, B On the Influence of Exercise on the Blood Sugar, Especially in Connection with Glucose Ingestion, *Acta med Scandinav* (supp) **55** 1, 1934 In this monograph and in the paper of F W Lapp and C L Torriani (*Blutzuckertagesablauf beim arbeitenden Diabetiker*, *Ztschr f klin Med* **117** 425, 1931) there are good bibliographies

9 Hetzel, K S, and Long, C N H The Metabolism of the Diabetic Individual During and After Muscular Exercise, *Proc Roy Soc, London*, s B **99** 279 (March 1) 1926

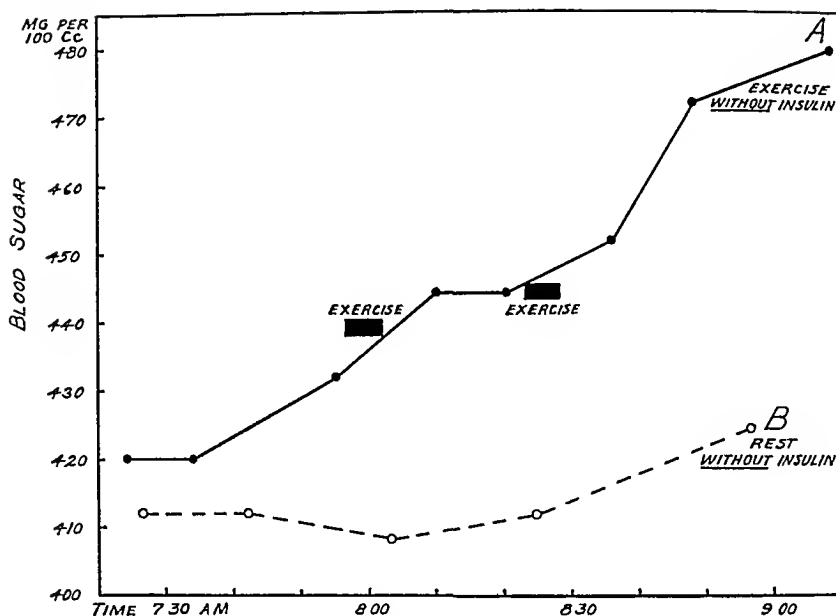


Chart 4 (case 4, R A) —Curve *A* No insulin had been given since a dose of 4 units at 10 p m, more than nine hours before the experimental period was begun on March 21. The two periods of exercise consisted of stair climbing for five minutes each. Curve *B* No insulin had been given since a dose of 4 units at 10 p m, over nine hours before the experimental period was begun on March 22, the patient being at rest during that time.

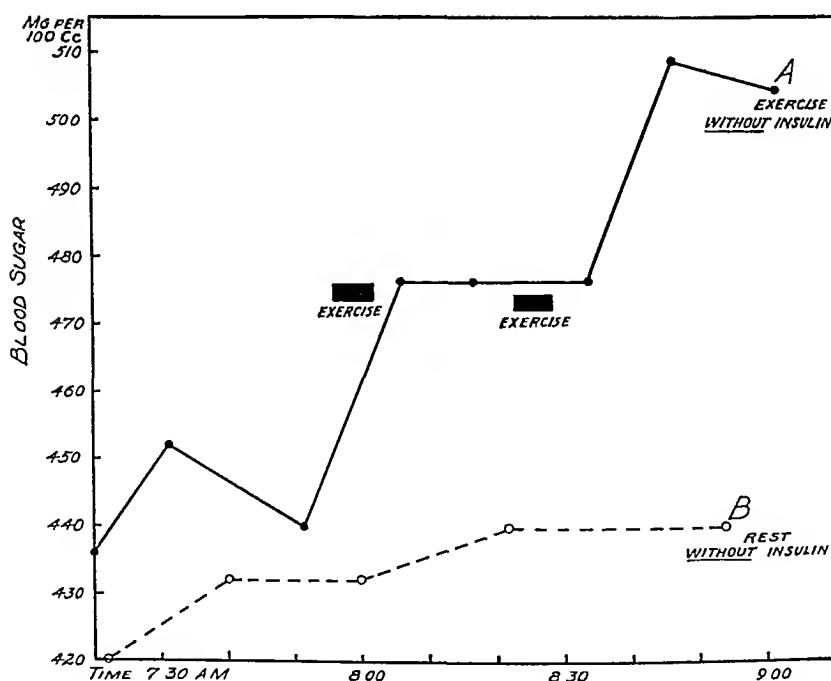


Chart 5 (case 5, T R) —Curve *A* No insulin had been given since a dose of 6 units at 10 p m, nine hours before the experimental period was begun on March 21. The exercise consisted of stair climbing for five minutes. Curve *B* No insulin had been given since a dose of 6 units at 10 p m, nine hours before the beginning of the experimental period, the patient being at rest during that time.

CASE 5—T R, a 138 year old boy, had had severe diabetes for nine and eight-tenths years. The diabetic condition was under good control with a diet of carbohydrate from 199 to 221 Gm, protein, 123 Gm, and fat, 106 Gm, and with 68 units of insulin a day. This patient was a diabetic pseudodwarf and, like the patient just discussed, had an enlarged liver, presumably filled with fat. The body weight was 60 pounds (27.3 Kg.)

This patient did exactly the same amount of stair climbing as the previous patient (case 4). The exercise tired him a trifle more, but the fatigue was slight and short lived. The results are shown in chart 5. In this case also exercise without insulin produced an unmistakable rise in the blood sugar value.

#### COMMENT

The foregoing results demonstrate that in the fasting patient with severe or moderately severe diabetes who has received no injection of insulin for several hours the immediate result of exercise may be that of raising the blood sugar level. This contrasts with the effect seen in the normal nondiabetic subject, in whom moderate exercise of short duration causes little if any change in the blood sugar content<sup>10</sup>. It is true that in normal persons more strenuous exercise, although it is of short duration, may cause a significant transient rise in the blood sugar content (*primare Arbeitshyperglycämie*<sup>11</sup>), but this is not nearly as marked or as constant as in the diabetic subject. Moreover, when the exercise is strenuous and prolonged, a decided decrease producing hypoglycemia may result<sup>12</sup>.

Exercise apparently stimulates the breakdown of glycogen in the liver, with a resulting outpouring of sugar into the blood stream. It is probable that this glycogenolysis is attributable in part to an increased secretion of epinephrine caused by the exercise. Thus, Hartman,<sup>13</sup> using the denervated pupil as an index, has shown that in normal cats there occurs an increase in the output of epinephrine during exercise on a treadmill. This is further borne out by the work of Cannon, Linton and Linton<sup>14</sup> and (at least for severe work) by that of Dill,

10 Trimble, H. C., and Maddock, S. J. The Fluctuations of the Capillary Blood Sugar in Normal Young Men During a Twenty-Four Hour Period (Including a Discussion of the Effect of Sleep and of Mild Exercise), *J. Biol. Chem.* **81** 595 (March) 1929.

11 Solandt, O. M., and Ferguson, G. C. The Effect of Strenuous Exercise of Short Duration upon the Sugar Content of the Blood, *Tr. Roy. Soc. Canada*, sect. 5, 1932, p. 173. Burger and Kramer<sup>5</sup>.

12 Levine, S. A., Gordon, B., and Derick, C. L. Some Changes in the Chemical Constituents of the Blood Following a Marathon Race, *J. A. M. A.* **82** 1778 (May 31) 1924. Best, C. H., and Partridge, R. C. Observations on Olympic Athletes, *Proc. Roy. Soc., London*, s. B **105** 323 (Sept. 2) 1929.

13 Hartman, F. A. The Relation of the Adrenals to Muscular Activity, *Endocrinology* **6** 511 (July) 1922.

14 Cannon, W. B., Linton, J. R., and Linton, R. R. Conditions of Activity in Endocrine Glands. XIV. The Effects of Muscle Metabolites on Adrenal Secretion, *Am. J. Physiol.* **71** 153 (Dec.) 1924.

Edwards and Mead<sup>15</sup> One must point out, however, that Katz<sup>16</sup> was unable to demonstrate in human subjects an increase in the epinephrine content of the blood during exercise

In the normal subject this flow of sugar from the liver is probably not as great as it is in the diabetic patient, since the stores of glycogen in the liver of the diabetic patient are comparatively less stable, furthermore, hyperglycemia is less severe because the sugar released is quickly used by the muscles In the completely diabetic organism, however, as has been shown by Yater and his co-workers,<sup>17</sup> contracting muscle is unable to utilize the dextrose molecule to obtain extra energy (although the dextrose requirement of the *resting* skeletal muscle is the same in the diabetic as in the nondiabetic state) These investigators regard it as a function of insulin to elaborate dextrose utilization by the muscle It seems reasonable to suppose that in the diabetic patient the unutilized sugar accumulates in the blood stream, producing the hyperglycemia noted in the studies reported in this paper

Richardson<sup>6</sup> found that although the diabetic subject with a normal blood sugar value during fasting responded to exercise in an essentially normal fashion, the patient with slightly more severe diabetes (with a fasting blood sugar value of approximately 175 mg per hundred cubic centimeters) showed after exercise an even greater drop than a normal subject He explained such results on the assumption that although the patient is able to withdraw sugar from the blood in a fashion approaching the normal, the glycogen stores of the body are not adequate to afford protection from hypoglycemia In our subjects no response of this type was observed Even in case 3, in which the blood sugar value during fasting varied from 120 to 188 mg per hundred cubic centimeters, definite increases in the blood sugar content were obtained after moderate exercise

It is evident that such studies bear a direct relationship to the treatment of diabetic patients In the first place, they point out definitely the value of adequate control of the diabetic condition The diabetic patient of today leads an essentially normal life, with an average amount of activity If the diabetic condition is imperfectly controlled and if the body has been supplied with an inadequate amount of insulin, then exercise instead of conferring benefit may actually increase the hyperglycemia and glycosuria

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15 Dill, D B , Edwards, H T , and Mead, S Blood Sugar Regulation in Exercise, *Am J Physiol* **111** 21 (Feb) 1935

16 Katz, G Ueber den Adrenalinhalt des peripheren menschlichen Blutes bei Muskelarbeit, *Ztschr f klin Med* **123** 154, 1933

17 Yater, W M , Markowitz, J , Cahoon, R F , and Burrows, W H Consumption of Blood Sugar by Muscle in the Nondiabetic and in the Diabetic State, *Arch Int Med* **51** 800 (May) 1933

Our results suggest another point with regard to treatment. For exercise to exert its maximum benefit sufficient insulin must be available in the body at the time of exercise. Practically speaking, after he arises in the morning the logical sequence for the diabetic patient is insulin, exercise and breakfast rather than exercise, insulin and breakfast. The exercise should be mild enough so that undue fatigue is not produced. The further advantage of two, three or more additional periods of exercise during the day is obvious.

In their studies on the effect of muscular exercise in two carefully controlled cases of uncomplicated diabetes, Soskin, Strouse and their colleagues<sup>18</sup> were unable to show "significant improvement in the diabetic tolerance or a decrease in the insulin requirements." Their results, although obtained for only two patients, were definite and unmistakable. One must agree, then, that exercise does not cause any fundamental change in the severity of the diabetic condition. (The improvement in physical fitness and muscular development produced by exercise will be conceded by all.) One knows, however, that by taking advantage of temporary decreases in the blood sugar content caused by insulin *plus exercise*, one may materially increase the amount of food given without any increase in the dosage of insulin. This was not brought out in the studies of Soskin and his associates, because their patients were kept on a constant diet and dosage of insulin. If, however, one gives additional food at those times of the day—commonly in the late forenoon, in the late afternoon and at bedtime—when by the combined effect of insulin and exercise the blood sugar value is lowest, one can easily demonstrate that on days of muscular activity much more food can be tolerated with the same or even a smaller amount of insulin than on days of relative inactivity. Priscilla White<sup>19</sup> has brought out this point strikingly in her studies of diabetic children at summer camps. One is impressed by the fact that under carefully controlled conditions, which include the accurate weighing of food, the frequent estimation of the blood sugar value and the daily determination of the quantity of sugar excreted in the urine, these young patients with severe diabetes tolerate more food and are in better health than during the winter, when for a large part of the day they are at school and inactive. To be sure, the exercise makes the diabetic condition no milder, and there is no significant lasting gain in tolerance which can be attributed to the exercise per se, but the end-result for the period of activity is the same, namely, the actual utilization of more food with the same or a lessened need for insulin.

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18 Soskin, S., Strouse, S., Molander, C. O., Vidgoff, B., and Henner, R. I. Value of Muscular Exercise in the Treatment of Diabetes Mellitus, *J. A. M. A.* **103** 1767 (Dec. 8) 1934.

19 White, Priscilla. Personal communication to the authors.



## SUMMARY

Exercise of short duration carried to the point of only mild fatigue invariably caused a definite and often a marked increase in the concentration of sugar in the blood of young patients with severe or moderately severe diabetes who had not received food or insulin for several hours

The practical bearing of this finding on the use of exercise in the treatment of diabetes is discussed

NOTE—Since the completion of the foregoing studies and the preparation of the manuscript, slowly-acting protamine insulinate has been introduced (Hagedorn, H C , Norman Jensen, B , Krarup, N B , and Wodstrup, I Protamine Insulinate, *J A M A* **106** 177 [Jan 18] 1936) It is evident that in this preparation, the effect of which lasts for from twelve to thirty hours, one has a means of keeping the level of the blood sugar of the patient with severe diabetes more nearly normal for a greater part of the twenty-four hours than is possible with regular insulin as ordinarily administered A patient receiving an adequate amount of protamine insulinate should always have some insulin available in the body Hence, exercise should exert a lowering effect on the blood sugar level in such a subject at practically all times

# CHOLESTEROL CONTENT OF BLOOD IN DIABETIC PATIENTS FED DIETS RICH IN FAT

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During recent years there has been increasing interest in the blood lipids in patients with diabetes mellitus, chiefly because of the uncertain relationship between dietary fat, hypercholesteremia and the frequent development of atherosclerosis in diabetic subjects. It has been repeatedly demonstrated that atherosclerosis can be produced in rabbits by feeding large amounts of cholesterol. It is also well known that many diabetic patients have hypercholesteremia, that atherosclerosis develops at a relatively early age in many diabetic patients and that this complication accounts for most of the incapacitation and fatality from this disease. The cause of a high cholesterol content of the blood and of vascular disease in diabetic patients has naturally been the subject of much investigation.

Before the advent of insulin it was necessary for all patients with diabetes except those with mild involvement to live on a high fat-low carbohydrate diet. Since 1922, with the use of insulin, a sharp restriction of carbohydrate has no longer been imperative. As a result, diets with less fat and more carbohydrate than were common in preinsulin days are being used in most clinics. During the change in trend from diets with a higher to those with a lower fat content there has been reported a general lowering of the cholesterol content of the blood. Joslin<sup>1</sup> has reported that the average cholesterol value for his diabetic patients fell from 385 mg per hundred cubic centimeters of blood in 1917 to 208 mg in 1934. He stated that this lower average value for cholesterol can be explained on the basis that the diets used in his clinic in recent years contained less fat and more carbohydrate than formerly. In fact, the opinion is prevalent that diabetic diets rich in fat cause hypercholesteremia and subsequently atherosclerosis.

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1 Joslin, E P, Root, H F, White, P, and Marble, A. The Treatment of Diabetes Mellitus, ed 5, Philadelphia, Lea & Febiger, 1935

Since the diabetic clinic of the University Hospital is one of the few which prescribe diets rich in fat, the cholesterol content was determined in a series of diabetic patients who had been on these diets, in order to determine whether there was any consistent relationship between the ingestion of fat and the level of cholesterol in the blood

#### METHOD

Only patients whose diabetes had been controlled for two months or longer while they had been eating the same diet were studied. The precaution that the diabetes be controlled was felt to be highly important, in order that the effects of hyperglycemia, glycosuria and acidosis on the cholesterol level of the blood would be eliminated. Female patients were studied in the intermenstrual period in order to avoid changes in the cholesterol content accompanying the menses.<sup>2</sup>

Specimens of blood taken during fasting were analyzed for cholesterol by the Windaus<sup>3</sup> gravimetric digitonide method during the early portion of the study, later the Okey<sup>4</sup> modification of this method, employing oxidation of the digitone, was used.<sup>5</sup> These two procedures gave similar results in our laboratory. The digitonin method of analysis was selected because of its greater accuracy as compared with the more commonly employed colorimetric method. Muhlbock and Kaufmann<sup>6</sup> have stated that the inaccuracies of the colorimetric method may vary from minus 18 to plus 76 per cent.

The essential information obtained in this study appears in the accompanying table, in which the data for twenty-one patients are listed according to the number of the dietary calories supplied by fat.

*The Normal Level of Cholesterol in the Blood*—It is difficult to know the true normal level of the cholesterol in the blood during fasting. Values given in the literature vary widely, owing chiefly to differences in the analytic methods employed. Digitonin methods for the determination of the cholesterol content ordinarily give values somewhat lower than methods based on the Liebermann-Burchard color reaction, because

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2 Okey, R., and Boyden, R. E. Studies of Metabolism of Women. Variations in Lipid Content of Blood in Relation to Menstrual Cycle, *J. Biol. Chem.* **72** 261 (March) 1927.

3 Windaus, S. Ueber die quantitative Bestimmung des Cholesterins und der Cholesterinester in einigen normalen und pathologischen Nieren, *Ztschr. f. physiol. Chem.* **65** 110, 1910.

4 Okey, R. A Micromethod for the Estimation of Cholesterol by Oxidation of the Digitonide, *J. Biol. Chem.* **88** 367 (Aug.) 1930.

5 In order to insure the complete extraction of lipids from the blood in each case the residue from the usual alcohol-ether extraction was ground in a mortar with fresh alcohol and ether, the mixture was then transferred to a beaker, heated to boiling, allowed to cool, filtered and washed twice with fresh alcohol and ether. This filtrate was then combined with the first extraction filtrate, and the analyses were carried out.

6 Muhlbock, O., and Kaufmann, C. Die gravimetrische Cholesterinbestimmung im Blut und Serum, *Biochem. Ztschr.* **233** 222, 1931.

certain products of decomposition of sterols give the color reaction with greater intensity than the sterol itself.<sup>7</sup> In a comparative study recently made by Gibbs, Buckner and Bloor<sup>8</sup> it was found that the colorimetric method gave results about 30 per cent higher than the Okey digitonin method. These investigators found the range of the cholesterol value in normal persons to be from 183 to 307 mg per hundred cubic

*Data for Twenty-One Diabetic Patients*

Patient	Sex	Age, Years	Other Diagnoses	Diet			Calories	Calories of Diet Derived from Fat, %	Calories of Metabolite Mixture* Derived from Fat, %	Length of Time Diabetes Was Controlled on This Diet	Daily Dose of Insulin, Units	Cholesterol Content of Blood, Mg per 100 Cc
				Protein, Gm	Fat, Gm	Carbohydrate, Gm						
F D J	M	36	None	58	274	63	2,947	84	84	8 yr	32	176
N K	M	40	Chronic sinusitis, psychoneurosis	55	250	60	2,700	83	83	2 mo	46	200
M T	F	60	None	55	220	65	2,460	81	81	5 yr	30	126
B W	F	19	None	55	220	65	2,460	81	81	3 yr	0	175
W M	F	15	None	55	220	95	2,500	80	80	5 mo	36	131
H B L	M	20	Undernutrition	70	320	120	3,600	80	76	3 mo	0	132
R N	M	17	None	70	260	80	3,000	80	80	8 mo	55	223
M T T	F	63	None	55	220	70	2,500	80	80	15 mo	36	202
J W	M	18	None	70	260	80	3,000	80	75	2 mo	0	167
Average								81				170
R H	F	59	None	55	155	45	1,800	78	78	4 yr	0	160
F F	M	44	None	55	175	45	2,000	78	84	2 mo	0	220
G L	M	49	Arteriosclerosis, chronic nephritis, neuroretinitis, slight obesity	55	200	115	2,500	73	73	3 yr	0	186
R D	M	16	None	55	200	95	2,460	73	73	3 yr	60	152
G B	F	15	None	50	160	90	2,000	72	72	20 mo	64	202
S F	M	18	None	55	220	150	2,800	71	71	20 mo	30	210
M E C	F	58	Hypertension, obesity	50	90	44	1,200	68	82	2 mo	0	223
M Mc	F	14	None	69	150	95	2,000	67	67	5 mo	45	173
L R	F	38	None	58	131	123	1,920	61	61	18 mo	36	203
M N	F	45	Hypertension	55	150	150	2,200	60	60	5 mo	0	165
R N S	F	44	Obesity, mild nephritis	50	65	110	1,200	49	74	2 mo	25	159
E S	F	58	Obesity, arterio sclerosis, incipient cataracts	52	50	90	1,000	43	74	2 mo	0	150
Average								66				185
Average for all cases												179

\* Estimated as described in the text

centimeters of plasma by the colorimetric method. In Joslin's clinic, where the colorimetric method is used, the normal range is considered to be from 100 to 230 mg per hundred cubic centimeters.<sup>1</sup> Different

7 Lifschutz, I. Die Abbauprodukte des Cholesterins in den tierischen Organen, *Ztschr f physiol Chem* **117** 201 (Dec.) 1921

8 Gibbs, C. B. F., Buckner, E., and Bloor, W. R. The Cholesterol to Cholesterol Ester Ratio in the Plasma of Diabetics with Advanced Arteriosclerosis, *New England J Med* **209** 384 (Aug 24) 1933

modifications of the digitonin precipitation method may give slightly different results. With a modified gravimetric digitonin method Man and Peters<sup>9</sup> found that the cholesterol values during fasting for ten normal persons ranged between 162 and 256 mg. With an oxidative digitonin method Boyd<sup>10</sup> recently found that the cholesterol values for normal young women range between 112 and 195 mg per hundred cubic centimeters of plasma, the mean being 162 mg. In this laboratory analysis of the blood of twenty-one normal persons from 18 to 62 years of age, equally divided as to sex, showed cholesterol values during fasting between 130 and 186 mg per hundred cubic centimeters of blood, the average being 156 mg.

In view of the foregoing discussion, it is readily seen that the interpretation of *small* differences in the cholesterol values of the blood is impossible and that a comparison of the values from different clinics is difficult because of the different methods used.

*The Relationship Between Dietary Fat and the Cholesterol Content*—The level of cholesterol in all the patients studied ranged from 126 to 223 mg per hundred cubic centimeters of blood, the average being 176 mg. It is seen that there is no correlation between the amount of fat in the diet and the cholesterol level of the blood. The following cases exemplify this lack of correlation. M. T., whose dietary fat furnished 81 per cent of the ingested calories, had a cholesterol value of only 126 mg per hundred cubic centimeters of blood, the lowest value observed, whereas M. E. C., whose dietary fat contributed only 68 per cent of the calorific value of the diet, had a cholesterol value of 223 mg per hundred cubic centimeters of blood, the highest value found (equal to that of R. N.).

Lack of any direct relationship between the amount of dietary fat and the level of cholesterol in the blood is further shown when average values are considered. Nine patients were on diets in which 80 per cent or more of the calorific value was supplied in the form of fat. The cholesterol values in this group ranged from 126 to 223 mg, the average value being 170 mg. This is especially significant when it is noted that the twelve patients whose dietary fat made up only from 43 to 78 per cent of the total caloric content had cholesterol values ranging from 150 to 223 mg, the average being 185 mg. The average cholesterol value was less in the diabetic patients who ingested the most fat.

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9 Man, E. B., and Peters, J. P. Gravimetric Determination of Serum Cholesterol Adapted to the Man and Gildea Fatty Acid Method, with a Note on the Estimation of Lipoid Phosphorus, *J. Biol. Chem.* **101** 685 (Aug.) 1933.

10 Boyd, E. M. A Differential Lipid Analysis of Blood Plasma in Normal Young Women by Micro-Oxidative Methods, *J. Biol. Chem.* **101** 323 (June) 1933.

Some of the patients studied were overweight and were accordingly on reduction diets. The metabolic mixture of each of these patients was calculated from the change in weight, assuming the caloric deficit to be made up entirely from body fat. The average cholesterol value of the blood in all whose metabolic mixture showed 80 per cent or more of the calories to be derived from fat (nine patients) was 186 mg per hundred cubic centimeters. The remainder, those whose metabolic mixture showed a range of from only 60 to 78 per cent of fat, had an average cholesterol value of 173 mg per hundred cubic centimeters. These average cholesterol values for the two groups differ by only 13 mg and lie within the range of the values for the control group.

One patient (F D J), a physician, had been on a diet of 58 Gm of protein, 274 Gm of fat and 63 Gm of carbohydrate for eight years. This diet had a fatty acid-dextrose ratio of 2.4 (as customarily calculated), and 84 per cent of the 2,947 calories was derived from fat. Certainly if ingestion of a diet rich in fat causes hypercholesteremia, one would expect it to develop in this case. Actually, however, the cholesterol content was only 176 mg per hundred cubic centimeters of blood, a normal value.

There has been considerable animal experimentation and clinical study concerning the possible relationship between dietary fat and the level of lipids in the blood. The results of such investigations are conflicting. Allen,<sup>11</sup> for instance, observed the effect of diet in dogs and described his results as follows:

Repeated and determined attempts were made to produce lipemia on the assumption that it might be the result of prolonged excess of fat or a preponderance of fat over carbohydrate or protein in the diet. One-sided fat diets were thus pushed to the point of producing peculiar fatal disturbances, to be described in detail later, but no significant grade of lipemia resulted in normal dogs, partially depancreatized non-diabetic dogs, or diabetic dogs free from glycosuria.

More recently Bloor<sup>12</sup> has found that "in both dogs and rabbits increasing the proportion of fat in the diet results in increased plasma phospholipoid and cholesterol, but in the dogs the increase is inconsiderable, while in the rabbits it is great."

Rabinowitch,<sup>13</sup> who has recorded the cholesterol values for a large number of diabetic patients under a great many different conditions,

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11 Allen, F. M. *Experimental Studies in Diabetes: The Production of Diabetic Lipemia in Animals, and Observations on Some Possible Etiologic Factors*, *J. Metabolic Research* **2**: 219 (Aug.) 1922.

12 Bloor, W. R. *Diet and the Blood Lipids*, *J. Biol. Chem.* **95**: 633 (March) 1932.

13 Rabinowitch, I. M. *Arteriosclerosis in Diabetes: I. Relationship Between Plasma Cholesterol and Arteriosclerosis, II. Effects of High Carbohydrate-Low Calorie Diet*, *Ann. Int. Med.* **8**: 1436 (May) 1935.

has said that he is convinced that the level of cholesterol in the blood is directly related to the fat of the diet. He stated "One of the most constant characteristics of the high carbohydrate-low caloric diet is an immediate and sustained decrease of plasma cholesterol." He pointed out that a number of factors contribute to hypercholesteremia, and of those other than the fat of the diet the lack of control of the disease is the most important.

In contrast, Boyd<sup>14</sup> found in his diabetic children that diets rich in fat (from 64 to 84 per cent of the energy value derived from fat) did not cause hypercholesteremia. Recently, Man and Peters<sup>15</sup> reported that in a study of seventy-nine diabetic patients on diets rich in fat the cholesterol value of the blood was normal in forty-two, above normal in twenty-eight and below normal in nine. Their diets contained, as a rule, from 125 to 175 Gm of fat. In an attempt to correlate the cholesteremia with dietary fat, they found it "impossible to relate either cholesterol or lipemia to fat intake." Their data are confusing in one respect, however, the blood sugar level was considerably above normal in many of the patients, indicating that the diabetic condition was not controlled in all cases. It is mentioned that no patient was dehydrated or acidotic.

Joslin<sup>1</sup> has repeatedly warned against the use of a diabetic diet rich in fat, inferring that such a diet would produce hypercholesteremia. Yet he<sup>16</sup> reports the personal observation of a patient who had lived for sixteen years on a diet low in carbohydrate, whose diabetes was controlled and who showed a cholesterol value which, much to his astonishment, was normal.

*Relationship Between Hypercholesteremia and Arteriosclerosis*—A number of years ago one of us (L. H. N<sup>17</sup>) reported the production of atherosclerosis in rabbits fed cholesterol. Some of the results of that study are of sufficient interest to be recalled in connection with this discussion. In a group of animals that received 113 mg of cholesterol daily the mean cholesterol value of the blood was normal (80 mg per hundred cubic centimeters). Four animals in this group had cholesterol values just above the highest value for a control animal, but in none of these was there evidence of atherosclerosis. The only animal of this group with an atherosclerotic aorta had a normal cholesterol

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14 Boyd, G. L. Blood Cholesterol in Diabetic Children, *Am J Dis Child* **38** 490 (Sept.) 1929.

15 Man, E. B., and Peters, J. P. Serum Lipids in Diabetes, *J Clin Investigation* **14** 579 (Sept.) 1935.

16 Joslin, E. P. Fat and the Diabetic, *New England J Med* **209** 519 (Sept 14) 1933.

17 Clarkson, S., and Newburgh, L. H. The Relation Between Atherosclerosis and Ingested Cholesterol in the Rabbit, *J Exper Med* **43** 595 (May) 1926.

value Of the group fed 250 mg of cholesterol daily for more than two hundred days, an atherosclerotic aorta was found in those with a normal as well as in those with a high blood cholesterol value, although the animal that exhibited the most extreme hypercholesteremia had a normal aorta Seven rabbits were fed 500 mg of cholesterol daily In all of these animals well marked hypercholesteremia developed, and five became atherosclerotic The statement was therefore made "It may be that there exists a causal relationship between the cholesterol in the blood and the state of the vessel, but we have not sufficient data dealing with the question to be in a position to give a final answer"

Such experiments, in which rabbits were fed cholesterol with the production of hypercholesteremia and later atherosclerosis, suggested that hypercholesteremia is a factor in causing arteriosclerosis in diabetic patients Yet there is no clearcut evidence that this is true Gibbs, Buckner and Bloor<sup>8</sup> have recently found slightly elevated cholesterol values in adult diabetic patients with arteriosclerosis However, it is not mentioned whether the diabetes was controlled in these patients It is noteworthy also that their patients with severe arteriosclerotic gangrene, necessitating amputation in many cases, were on diets with only 55 per cent of fat

Joslin<sup>10</sup> stated that arteriosclerosis was fifteen times as frequent in his diabetic children who showed hypercholesteremia as in the group who had normal cholesterol values In adult diabetic patients with arteriosclerosis studied in Joslin's clinic high cholesterol values were not found In fact, in one study<sup>18</sup> it was observed that the cholesterol value was lowest in those patients who showed the most marked arteriosclerosis In a recent study Man and Peters<sup>15</sup> found that severe arteriosclerosis with or without hypertension was evident in patients with cholesterol values that were normal, below normal and above normal, and they were unable to find any relationship between the level of the cholesterol and the degree of arteriosclerosis

In this connection it is of interest to note that of the twenty-one patients who were the subject of this study only eight showed cholesterol values higher than our normal range—and these were only slightly higher The highest value observed was 223 mg per hundred cubic centimeters There appeared to be no relation to the age of the patient, the ages were scattered between 15 and 63 years There were four males and four females It was previously pointed out that the cholesterol values could not be correlated with the amount of fat in the diet What is the significance of the cholesterol values that were slightly higher than those in the normal subjects? Are cholesterol values of

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18 Hunt, H M Cholesterol in Blood of Diabetics Treated at the New England Deaconess Hospital, *New England J Med* 201 659 (Oct 3) 1929



this level in any way injurious to the patient? We are unable to answer these questions with certainty. It should be noted, however, that in none of the patients whose cholesterol value was slightly higher than normal was evidence of arteriosclerosis revealed by careful physical examination. The two persons who had arteriosclerosis had cholesterol values of 150 and 186 mg per hundred cubic centimeters, respectively.

*The Effect of Controlling the Diabetes on the Level of the Blood Lipids*—The confusion in the literature regarding the relationship of ingestion of fat, marked hypercholesteremia and arteriosclerosis exists, in our opinion, chiefly because most investigators do not discriminate between diabetic patients whose disease is controlled and those in whom hyperglycemia, glycosuria and ketonuria exist. The factor of primary importance in the prevention of marked hypercholesteremia and hyperlipidemia is *control of the diabetes*. This was vividly demonstrated by the work of Marsh and Waller,<sup>19</sup> who showed repeatedly that the hyperlipemia existing in patients with uncontrolled diabetes promptly disappeared as the diabetes became controlled, even though concurrently the fat of the diet was progressively increased from 85 to over 200 Gm. That controlling the diabetes is the important factor in eliminating hyperlipemia is likewise splendidly shown by the work of Curtis, Sheldon and Eckstein.<sup>20</sup> These investigators controlled severe diabetes in a boy *on a diet rich in fat* and measured the steady decline in the lipoids from 14 to 1.4 per cent. Then, keeping the fat of the diet constant *at 300 Gm*, they allowed the diabetes to become uncontrolled by omitting insulin. Hyperglycemia, intense glycosuria and ketonuria developed, and simultaneously hyperlipemia occurred. All these abnormalities promptly disappeared when the diabetes was again controlled by the use of insulin.

At the beginning of this article reference was made to the fall in the average cholesterol values for the patients in Joslin's clinic during the past twenty years. That diabetes is better controlled now than in previous decades is shown in many ways, probably most strikingly by the huge decrease in the deaths due to coma. Joslin's statistics show that only 6.1 per cent of his patients died in diabetic coma between 1930 and 1935, as against 60.8 per cent between 1898 and 1914. It is our opinion that rather than explain the decrease in the average cholesterol value during the past two decades by the change to diets with lower fat and a higher carbohydrate content it would be more correct to explain the decrease on the basis of the greater success in controlling the disease.

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19 Marsh, P. L., and Waller, H. G. The Relation Between Ingested Fat and the Lipemia of Diabetes Mellitus, *Arch Int Med* **31** 63 (Jan) 1923.

20 Curtis, A. C., Sheldon, J. M., and Eckstein, H. C. Experimental Reproduction of Lipemia, *Am J M Sc* **136** 548 (Oct) 1933.

## CONCLUSIONS

In twenty-one patients with *controlled* diabetes who were on diets rich in fat for from two months to eight years, the cholesterol values of the blood during fasting were found to range between 126 and 223 mg per hundred cubic centimeters, the average being 176 mg. In the same number of normal control subjects the values ranged between 130 and 186 mg per hundred cubic centimeters, the average being 156 mg.

The level of cholesterol in the blood of these diabetic patients could not be correlated with the amount of fat in the diets.

Values only *slightly* higher than the highest ones for the control subjects were found in eight of the twenty-one subjects. The significance of these higher values is not clear.

Lack of control of the diabetes appears to be the major factor in the causation of hypercholesteremia in diabetic patients.

# PNEUMOCOCCUS TYPE II AND TYPE V INFECTIONS

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The separation of types among the pneumococci previously included in group IV<sup>1</sup> has made it possible properly to classify pneumococci from practically all sources,<sup>2</sup> thus affording a more rational attack on various epidemiologic,<sup>3</sup> immunologic<sup>4</sup> and clinical<sup>5</sup> aspects of pneumo-

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This study was aided, in part, by a grant given in memory of Francis Weld Peabody by the Ella Sachs Plotz Foundation

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2 (a) Raia, A , Plummer, N , and Shultz, S New Types of Pneumococci in the Pneumonias of Children, *Am J Dis Child* **42** 57 (July) 1931 (b) Gundel, M , and Seitz, L Die Pneumokokkentypen in der gesunden Bevolkerung, *Klin Wchnschr* **12** 929, 1933 (c) Bullowa, J G M , Sommers, M , and Turner, E The Reliability of Sputum Typing and Its Relation to Serum Therapy, *J A M A* **105** 1512 (Nov 9) 1935

3 (a) Webster, L T , and Hughes, T P The Epidemiology of Pneumococcus Infection The Incidence and Spread of Pneumococcus in the Nasal Passages and Throats of Healthy Persons, *J Exper Med* **53** 535, 1931 (b) Smillie, W G The Epidemiology of Lobar Pneumonia A Study of the Prevalence of Specific Strains of Pneumococci in the Nasopharynx of Immediate Family Contacts, *J A M A* **101** 1281 (Oct 21) 1933 (c) Gundel and Seitz<sup>2b</sup>

4 Winkler, A W , and Finland, M Antibody Response to Infections with the Newly Classified Types of Pneumococci (Cooper), *J Clin Investigation* **13** 109, 1934

5 Sutliff, W D , and Finland, M The Significance of the Newly Classified Types of Pneumococci in Disease Types IV to XX Inclusive, *J A M A* **101** 1289 (Oct 21) 1933

coccic infections and their specific treatment<sup>6</sup> It has made possible also the segregation of pneumococci previously recognized primarily because of their relationship to other types<sup>7</sup> The antibody response to infections with such related types and the immunologic reactions of normal human subjects to these pneumococci have already received some attention<sup>8</sup> The clinical and bacteriologic features of the disease produced by type III and the related type VIII pneumococci have been reported from two different clinics<sup>9</sup> This paper deals with the more important features of infections with type II and the related type V pneumococci, with especial reference to pneumonia

The type II pneumococcus ranks second or third in frequency as a cause of pneumonia The actual incidence in different series of cases of pneumococcic lobar pneumonia has varied from 10.9 per cent<sup>10</sup> to 32.7 per cent,<sup>11</sup> with a mortality rate of from 30 to 49 per cent in large

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6 Bullowa, J. G. M. (a) The Therapeutic Value of Specific Type VII (Cooper) Antipneumococcus Serum, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 1, p. 283, (b) Pneumonias Due to Pneumococcus Type VIII, *Am. J. M. Sc.* **190**: 65, 1935, (c) Pneumonia Due to Pneumococcus Type XIV (Cooper) and Its Treatment with Specific Serum, *J. Clin. Investigation* **14**: 373, 1935

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8 (a) Finland, M., and Winkler, A. W. Antibody Response to Infections with Type III and the Related Type VIII Pneumococcus, *J. Clin. Investigation* **13**: 79, 1934, (b) Antibody Responses to Infections with Type II and the Related Type V Pneumococci, *ibid.* **13**: 97, 1934. (c) Finland, M., and Sutliff, W. D. Immunity Reactions of Human Subjects to Strains of Pneumococci Other Than Types I, II and III, *J. Exper. Med.* **57**: 95, 1933

9 (a) Finland, M., and Sutliff, W. D. Infections with Pneumococcus Type III and Type VIII. Characterization of Pneumonia Caused by Pneumococcus Type III and That Associated with a Biologically Closely Related Organism, Pneumococcus Type VIII, *Arch. Int. Med.* **53**: 481 (April) 1934. (b) Bullowa<sup>6b</sup>

10 Thomas, W. S. Type I Pneumonia and Its Serum Treatment, *J. A. M. A.* **77**: 2101 (Dec. 31) 1921

11 Griffith, F. Serological Types of Pneumococci in Lobar Pneumonia. A Study of One Hundred Cases, *Lancet* **2**: 226, 1921

groups of patients who did not receive serum treatment<sup>12</sup> This type has been said to give rise, with great regularity, to the typical clinico-anatomic picture of lobar pneumonia,<sup>13</sup> as distinguished from the so-called atypical forms<sup>14</sup> or bronchopneumonia It is uncommon in pneumonia of childhood<sup>2a</sup> Type II is rarely present in the normal nasopharynx except in persons who have come in contact with patients suffering from pneumonia due to this type<sup>15</sup> It is likewise uncommon in cases of focal infection in the absence of pneumonia<sup>5</sup> It is of added importance because there is evidence to indicate that patients with pneumonia due to this type of pneumococcus are benefited by the proper use of homologous antiserum<sup>16</sup>

The type V pneumococcus is the most frequent and the most pathogenic of the types of pneumococci formerly recognized by their atypical reactions with type II antiserum<sup>17</sup> In the past many instances of type V infection have probably been classified with cases of type II infection, a matter of some consequence, particularly in the evaluation of specific serum therapy With the more accurate identification by means of specific agglutinating serums, the type V pneumococcus has been shown to be one of the most frequent of the new types present in cases of pneumonia<sup>18</sup> It rarely occurs in the normal nasopharynx<sup>3</sup> It was considered to be the causative agent in an institutional outbreak of colds, bronchitis and pneumonia<sup>19</sup> Strains of this type have a greater tendency than others to hemolyze blood cells added to broth culture mediums, which may explain the large percentage of positive results of blood cultures in cases of type V infection<sup>1b</sup>

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12 (a) Park, W H, Bullowa, J G M, and Rosenbluth, M B The Treatment of Lobar Pneumonia with Refined Specific Antibacterial Serum, *J A M A* **91** 1503 (Nov 17) 1928 (b) Cecil, R L, and Plummer, N Pneumococcus Type II Pneumonia A Clinical and Bacteriological Study of One Thousand Cases, with Especial Reference to Serum Therapy, *ibid* **98** 779 (March 5) 1932

13 Gundel, M Die Bakteriologie, Epidemiologie und spezifische Therapie der Pneumokokkeninfektionen des Menschen unter besonderer Berücksichtigung der Pneumonie, *Ergebn d Hyg, Bakt, Immunitätsforsch u exper Therap* **12** 133, 1931

14 Cole, R I Acute Pulmonary Infections, De Lamar Lectures, 1927-1928, Baltimore, Williams & Wilkins Company, 1928

15 Smilie<sup>3b</sup> Gundel and Seitz<sup>2b</sup>

16 (a) Finland, M, and Sutliff, W D The Specific Serum Treatment of Pneumococcus Type II Pneumonia, *J A M A* **100** 560 (Feb 25) 1933 (b) Cecil and Plummer<sup>12b</sup> Other writers have reported similar results

17 Stillman, E G A Study of Atypical Type II Pneumococci, *J Exper Med* **29** 251, 1919 Avery<sup>7</sup>

18 Cooper and others<sup>1b</sup> Bullowa, Sommers and Turner<sup>2c</sup> Sutliff and Finland<sup>5</sup>

19 Schroder, M C, and Cooper, G An Epidemic of Colds, Bronchitis and Pneumonia Due to Type V Pneumococci, *J Infect Dis* **46** 384, 1930

## PATIENTS INVESTIGATED AND SOURCES OF PNEUMOCOCCI

Since November 1929 all pneumococci obtained at the Boston City Hospital from sputum, blood or pus or from various sources at autopsy were classified with the aid of the new typing serums<sup>1</sup> obtained from Dr William H Park and Miss Georgia Cooper. For rapid typing of sputum the Sabin method<sup>20</sup> and, during the last two years, the *Quellung* reaction of Neufeld<sup>21</sup> have been utilized. These were checked as a routine by standard methods<sup>22</sup>. Strains of type II and type V pneumococci were cross-agglutinated in serums of both these types before they were definitely classified. Between Nov 1, 1929, and May 31, 1935, pneumococci were obtained from a total of 2,950 patients. Type II pneumococci were obtained during this period from 263 patients and type V from 162 patients, an incidence

TABLE 1—*Conditions Associated with Type II and Type V Pneumococci at the Boston City Hospital, November 1929 to May 1935*

Disease	All Cases				Autopsies			
	Type II Pneumococci		Type V Pneumococci		Type II Pneumococci		Type V Pneumococci	
	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent
Lobar pneumonia	219	83.3	107	66.0	38	71.7	22*	47.8
Bronchopneumonia	15	5.7	33	20.4	10	18.9	20	43.5
Empyema (present at entry)	12	4.6	6	3.7			1	2.1
Infections without pneumonia								
Otitis media and/or mastoiditis	4		4		1		1	
Meningitis	1		2		1		1	
Osteomyelitis	2							
Peritonitis			3					
Abscess of neck	1							
Bacteremia (no focus found)	3				3			
Pulmonary abscess			1				1	
Total	11	4.2	10	6.2	5	9.4	3	6.5
Infection of the upper respiratory tract	4	1.5	2	1.2				
Pulmonary tuberculosis	2	0.8	2	1.2				
Routine nasopharyngeal cultures			2	1.2				
Total number of cases	263	100.0	162	100.0	53	100.0	46	100.0

\* In 3 of these cases there was also some patchy infiltration in other portions of the lung

of 8.2 and 5.5 per cent, respectively, of all cases of pneumococcal infection. Autopsies were performed in 53 of the cases of type II and in 46 of the cases of type V infection. The hospital records, roentgenograms and autopsy protocols were all utilized and correlated with the bacteriologic observations. Permission to use the bacteriologic and pathologic data was granted by Drs Frederic Parker Jr and Robert N Nye, of the Mallory Institute of Pathology.

20 Sabin, A. B. Microscopic Agglutination Test in Pneumonia, *J. Infect. Dis.* **46**: 469, 1930.

21 Sabin, A. B. Immediate Pneumococcus Typing Directly from Sputum by the Neufeld Reaction, *J. A. M. A.* **100**: 1584 (May 20) 1933.

22 Avery, O. T., Chickering, H. T., Cole, R., and Dochez, A. R. Acute Lobar Pneumonia. Prevention and Serum Treatment, Monograph 7, Rockefeller Institute for Medical Research, 1917.

The conditions which could be attributed to the type II and V pneumococci are listed in table 1. The intimate association of both these types with pneumonia is apparent. In 93.6 per cent of the patients with type II pneumococci and in 90.1 per cent of those with type V pneumococci there was either pneumonia or empyema attributed to these organisms.

#### CONDITIONS OTHER THAN PNEUMONIA

The pneumococci from the patients with infection of the upper respiratory tract and from the patients with pulmonary tuberculosis, noted in table 1, were obtained from the sputum. A case of tonsillitis with type II pneumococci is included among the former cases. Tubercle

TABLE 2—*Focal Infections with Type II and Type V Pneumococci*

Case	Sex	Age, Years	Focal Infection	Outcome	Remarks*
Type II Infection					
1	F	4	Mastoiditis	Died	S Au from other ear and meninges
2	M	23	Mastoiditis	Died	Also S H sepsis
3	M	4	Otitis media	Lived	
4	F	9	Mastoiditis	Lived	After scarlet fever
5	M	56	Meningitis	Died	Pn II bacteremia, treated with Felton's serum
6	M	70	Abscess of neck	Died	
7	M	14	Osteomyelitis	Lived	Began as cellulitis
8	F	3	Osteomyelitis	Lived	S Au cultured before
Type V Infection					
1	M	1	Mastoiditis	Died	After scarlet fever, S H in blood and other ear
2	F	6	Otitis media	Died	S H in blood and meninges
3	F	2	Mastoiditis	Lived	
4	M	5	Mastoiditis	Lived	
5	F	8	Meningitis	Died	After otitis media
6	M	8	Meningitis	Died	
7	M	55	Lung abscess	Died	Also S Au and B coli, in carcinoma of lung
8	M	2	Peritonitis	Lived	With appendicitis
9	F	44	Peritonitis	Lived	With pyosalpinx
10	M	11	Peritonitis	Lived	Ruptured appendix

\* For the key to the abbreviations see table 4.

bacilli were demonstrated in the sputum of all but 1 (also a case of type II infection) of the 4 tuberculous patients, none of whom gave definite evidence of any acute infection which could be attributed to the pneumococci. In 2 patients type V pneumococci were obtained from the nasopharyngeal cultures made as a routine, for hemolytic streptococci in one instance and for diphtheria bacilli in the other. Neither of these patients had an active infection. There were no deaths among this group of patients.

In the patients admitted to the hospital with empyema and in those with focal infection the pneumococci were isolated from cultures of pus obtained directly from the lesions. In the 3 cases of so-called bacteremia the pneumococci were obtained from cultures of the heart blood made at autopsy. One of these patients was a premature infant who died as a

result of progressive jaundice and diarrhea, the second was a 2 month old infant with congenital syphilitic cirrhosis of the liver and jaundice, and the third was a woman of 60 who died shortly after being admitted to the hospital because of a relapse of pernicious anemia. In none of these 3 patients was any evidence of infection present in any organ.

All the patients who had empyema at the time of admission to the hospital were treated with open drainage by rib resection. Death occurred in 2 such cases of type II infection in patients aged 83 and 27 years, respectively, and in 2 cases of type V infection in patients aged 80 and 47 years, respectively. The fatal cases were all in males. Of the surviving patients with empyema due to type II pneumococci, 7 were less than 15 years old and the others were aged 21, 42 and 50 years, respectively. Only 1, an infant, was a female, the others were males. The patients with empyema due to type V pneumococci who recovered, 1 male and 3 females, were all under 14 years of age.

Some of the features in the cases of other purulent focal infections are listed in table 2. Other organisms were often cultured from material from the same patient, streptococci and staphylococci being the most common. The deaths in the cases of infection of the middle ear and of the mastoid were probably due to invasion by streptococci.

The remainder of this paper will be devoted to a consideration of the clinical and bacteriologic aspects and pathologic observations of the pneumonia associated with type II and V pneumococci. Specific anti-serum was used in some of the cases of type II infection which were therefore segregated in calculating mortality percentages. The effects of serum therapy are analyzed elsewhere<sup>23</sup>

#### PNEUMONIA DUE TO TYPE II AND TYPE V PNEUMOCOCCI

The sources from which the type II and type V pneumococci were obtained in the cases of pneumonia are noted in table 3. In half the patients with pneumonia these pneumococci were obtained from sources other than the sputum, which indicated a definite etiologic relationship to this disease. In about one fifth of the patients in whom the sputum was the only source of the pneumococcus the same type was obtained from 2 or more specimens. In all, type II pneumococci were identified in 524 specimens and type V in 319 specimens of various materials obtained from patients with pneumonia.

#### MIXED INFECTIONS

The clinical significance of isolating pneumococci of more than one type or of isolating pneumococci and other significant organisms from

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23 (a) Finland, M., and Dowling, H. F. The Dose of Antibody Effective in the Treatment of Pneumococcus Type II Pneumonia, *Am J M Sc* **191** 658 (May) 1936. (b) Finland and Sutliff<sup>16a</sup>



patients with pneumonia has been discussed elsewhere<sup>24</sup> Immunologic studies have indicated that some pneumococci, particularly types I and II, when they are obtained in cases of pneumonia along with other types of pneumococci, are more likely to be the significant etiologic agent than others, particularly type III pneumococci In the present series other types of pneumococci were obtained from 4 of the patients with type II pneumonia and from 7 of the patients with type V pneumonia, an incidence of 17 and 5 per cent, respectively All other significant organisms, including pneumococci, were found in 20 of the cases of type II pneumonia and in 21 of the cases of type V pneumonia, constituting 85 and 15 per cent, respectively, of the cases of pneumonia due to these types

TABLE 3—*Sources of Type II and Type V Pneumococci Obtained in Cases of Pneumonia*

Source	Type II		Type V	
	Cases	Per Cent	Cases	Per Cent
Single specimen of sputum	97	41.4	55	39.3
Multiple specimens of sputum	27	11.5	15	10.7
Blood or pus	11	4.7	15	10.7
Autopsy	17	7.3	20	14.3
Autopsy and antemortem cultures	21	9.0	17	12.1
Multiple sources during life	61	26.1	18	12.9
Total	234	100.0	140	100.0
At autopsy				
Heart blood	23		21	
Lungs	31		30	
Pus (all foci)	17		17	
No cultures made	8		5	

A study of the sources of the various organisms listed in table 4 indicates that the rôle of other pneumococci, when found with either type II or type V strains, was probably a minor one Further evidence for such an assumption was adduced from immunologic studies in some of these cases which indicated that only the type II or V pneumococci were antigenically active<sup>25</sup> Streptococci and staphylococci, on the other hand, were usually secondary invaders causing "superinfections," although in some instances, when they were obtained only from the sputum, they were probably not related to the pulmonary infection The rôle of *Haemophilus influenzae* was difficult to evaluate The patients with tubercle bacilli noted in table 4 all had typical lobar pneumonia complicating active pulmonary tuberculosis, in contrast to the cases noted in table 1 in which there was no acute infection attributable to the pneumococcus

<sup>24</sup> Finland, M The Significance of Mixed Infections in Pneumococcal Pneumonia, *J A M A* 103 1681 (Dec 1) 1934 Winkler and Finland<sup>4</sup>

TABLE 4—*Mixed Infections in Cases of Pneumonia Due to Type II and Type V Pneumococci*

Case	Pneumonia*		Sources of Homologous Type of Pneumococcus†	Other Organisms‡	Sources
	Kind	Outcome			
Type II infection					
1	L	R 6	S 3, 4, B 3	B M C Pn IV	S 3, 4 S 11, 12
2	L	D 10	S 6, Perle	Pn III	Rll
3	B	R-5	S 3	Pn III	S 3
4	L	D 9	B 7	Pn XX	S-8
5	L	D ?	Rll	S H	Rll
6	L	D 7	S 3, B 3	S H	S 6
7	L	D 7	S 3, B 3, 6, H, all lobes	S H	Lul
8	B	D ?	Lll	S H	H, Lll
9	B	D 2	Rll, Lll	S H	Rll, Lll
10	B	D 7	Rll	S H	Rll, Rul, Lll
11	L	R 6	S 5	S Au	Cervical abscess 17
12	L	R ?	S 2, B 3	S Au S H	S 21, 36, B 6, 9, ear 10, 19 B 18, ear 19, C 22, 23
13	L	R-7	S 3	S H, S Au	Ear 17
14	B	D 3	S-1	S H, S Au	S 1
15	L	R-17	S 16	H I	S 15
16	L	D 10	S 6, B 6, H, Rll, Lll	H I	Rll, Lll
17	L	D 12	S 3, B 3, 8, 10, 4 lobes	S V	3 lobes (1 without Pn II)
18	L	R-8	S 6, B 7	T B	6 times
19	L	R-14	S 11	T B	4 times
20	L	R 17	S 17	T B	3 times
Type V infection					
1	L	R 6	S 5	Pn III	S 9
2	L	R 8	S 13, 16	Pn III, H I	S 11
3	L	D 33	S 9, C 16, 23, 30	Pn X	S 6
4	L	D 4	S-4, H, C, Rll, Rul, Lll	Pn X	Lll
5	L	R-8	S 30	Pn XI	S 3
6	B	D 12	Rll	Pn XIV	S 2, 3
7	B	D 12	Rll, Lll	XVIII, S H	S 8
8	L	D 11	S 6, 10, B 6, 10, C (Rt )	S H	Abd, C (left)
9	B	D 12	Mastoid	S H	B-7, 9, H
10	L	R ?	S 4, B 4	S H	C 16, throat 21
11	L	D 13	S 12	S H	S 6
12	B	D ?	Rll	S H, B coli	Lll
13	B	D 11	S 1, 7, B 7, 8	S H	B 10
14	L	R ?	C 15, 17, 30, 38, 42	S Au	Throat 7, 8
15	L	R-?	C 9, 12, 17	S H, S Au	C 21
16	L	R 16	S 14	S H, S Au	S 15
17	B	D 2	S 1	S H S Au B coli	H, Rll, C, Abd Rll, C Abd, kidney
18	L	D 6	Rll	S H S Au	H, Rll Rll
19	B	R 4	S 3	H I	S 3
20	B	D 16	S 5, 6, 7, Rll	H I	S 5, 6, 7
21	L	D 19	S 14	S H, H I	Rll

\* L indicates lobar pneumonia, B, bronchopneumonia, R, recovered, and D, died, and the numbers represent the day of the disease on which the study was made

† S indicates sputum, B, blood, C, pleural exudate, Rll, lower lobe of right lung, Lll, lower lobe of left lung, Rul, upper lobe of right lung, Lul, upper lobe of left lung, Perle, perleardial exudate, Abd, peritoneal exudate, and H, heart blood, and the numbers represent the day of the disease. When no number is given, the cultures were made at autopsy

‡ Pn indicates pneumococcus (type is given in Roman numerals), B M C, Bacillus mucosus capsulatus, S H, beta hemolytic streptococcus, S Au, hemolytic Staphylococcus aureus, H I, Haemophilus influenzae, S V, Streptococcus viridans, and T B, tubercle bacilli (sputum smears)

## SEASONAL INCIDENCE

The month of the highest incidence, as noted with regard to type III and type VIII pneumonia,<sup>9a</sup> differed from year to year. It always occurred between January and March. It was usually the same for type II as for type V pneumonia and corresponded to the month when types I, III and VIII pneumonia also were most frequent. In some years there was more than a proportionate number of cases of one type or another during the peak month. During some months, also, there was a disproportionate increase in the number of cases of one type independent of the general peak of incidence. The largest number of patients with each type of pneumonia admitted in any one month was 17 with type II pneumonia in March 1932 and 12 with type V pneumonia in January 1933. The annual incidence showed decided varia-

TABLE 5—*Annual Incidence of Infections Due to Type II and Type V Pneumococci*

Year	All Cases		Pneumonia and Empyema	
	Type II	Type V	Type II	Type V
1929-1930	51	13	48	13
1930-1931	60	20	56	19
1931-1932	55	17	52	16
1932-1933	54	55	47	50
1933-1934	25	31	25	25
1934-1935	18	26	18	23
All years	263	162	246	146

tions (table 5), although the total number of cases of pneumococcic pneumonia for each year was fairly constant over the period of this study.

## AGE AND SEX INCIDENCE WITH RELATION TO MORTALITY

The number of patients with type II and type V pneumonia, arranged according to age and sex, are shown in table 6. The mortality in each group is noted. The patients under 10 years of age are not comparable with the rest of the patients since no special effort was made to study them bacteriologically. The type of pneumococcus in these cases was determined only from organisms obtained from the blood, pleural fluid or autopsy materials. Partly for this reason and partly also because a number of infants were included, the percentage mortality in this age group is inordinately high. Briefly, the age distribution was closely similar in the cases of type II and of type V lobar pneumonia, except for the greater incidence of children under 10 years of age. The mortality figures for the cases of type V pneumonia also show a striking similarity within the various age groups, to those found in the cases of

type II pneumonia in which serum was not given. There was a distinctly smaller proportion of females among the patients with type II pneumonia than among those with type V pneumonia. The mortality rate was the same among males and females in each group.

COMPARISON OF THE INCIDENCE AND MORTALITY IN LOBAR PNEUMONIA AND BRONCHOPNEUMONIA DUE TO TYPE II AND TYPE V PNEUMOCOCCI

Particular care has been taken throughout this study to classify the cases of pneumonia according to the character of the lesion in the lung.

TABLE 6—*Analysis of Incidence and Mortality of Pneumonia Due to Type II and Type V Pneumococci*

Cases		Age, Years		Lobar Pneumonia												Bronchopneumonia											
				Type II								Type V				Type II								Type V			
				Serum			No Serum			All	Type II					Type II			Type V								
				Number	Died	Died, per Cent	Number	Died	Died, per Cent	Incidence, per Cent	Number	Died	Died, per Cent	Incidence, per Cent	Number	Died	Died, per Cent	Incidence, per Cent	Number	Died	Died, per Cent	Incidence, per Cent					
All cases	86	27	31	133	64	48	94†	107	46	43	74†	15	12	80	6†	33	24	73	26†								
<10 years*							0	4	1	25	4	3	2	20	6	5			18								
10-19 years	12	1	8	13	1	8	11	12	1	8	11	1	1	7	2	0			6								
20-29 years	21	4	19	22	8	36	20	16	5	31	15	0	0	0	2	2			6								
30-39 years	21	7	33	27	7	26	22	28	8	29	26	3	2	20	4	2			12								
40-49 years	15	5	33	29	18	62	20	17	9	53	16	1	0	7	6	6			18								
50-59 years	14	8	57	22	14	64	16	17	11	65	16	2	2	13	3	1			9								
60-69 years	3	2	67	16	12	75	9	9	7	78	8	2	2	13	7	6			21								
70+				4	4	100	2	4	4	100	4	3	3	20	3	2			9								
Males	73	24	33	111	51	46	84	76	32	42	71	13	11	85	87	19	13	79	58								
Females	13	3	23	22	13	59	16	31	14	45	29	2	1	50	13	14	11	68	42								
Primary	82	23	28	126	60	48	95	100	42	42	93	1	1	100	7	14	10	71	42								
Secondary	4	4	100	7	4	57	5	7	4	57	7	14	11	79	93	19	14	74	58								
Mixed infections	6	4	67	9	3	33	7	13	6	46	12	5	4	80	33	8	7	88	24								

\* Study limited to medical cases (patients over 12 years of age). The bacteriologic data were available for only a small number of the patients less than 12 years of age.

† Per cent of all cases of pneumonia of this type. Other percentages refer to lobar or bronchopneumonia.

In this respect, the autopsy observations, when available, were considered the most significant, and the roentgen and physical findings, in the order mentioned, were considered next in importance. Only rarely, however, were the findings in disagreement. For purposes of classification all cases in which the pulmonary lesion was atypical, that is, not uniform in distribution, were called instances of bronchopneumonia. The relative frequency with which such cases were encountered is shown in table 6. In addition, the numbers of cases are listed in this table according to age, sex, primary and secondary pneumonia and mixed infections. The percentage of incidence and of mortality is noted for each group.

Atypical pneumonia is relatively more common among patients with type V pneumococcic pneumonia than among those with type II pneumonia, about 1 in every 4 of the former and 1 in every 16 of the latter having bronchopneumonia. There was a greater percentage of persons over 60 years of age with bronchopneumonia than with lobar pneumonia. The mortality among the patients with bronchopneumonia varied only slightly with age, whereas among the patients with lobar pneumonia the mortality showed the usual increase with advancing age. Except among persons over 60 years of age, the mortality was always higher among the patients with bronchopneumonia. This greater number of deaths is due, in large part, to the fact that in most cases bronchopneumonia was secondary to some other serious acute disease, while in most cases of lobar pneumonia the pneumonia was primary. There were relatively more female patients among those with type V bronchopneumonia than among those with lobar pneumonia. Mixed infections were more common and associated with a higher mortality among the patients with bronchopneumonia.

#### PREDISPOSING FACTORS

Some of the common conditions within the patient which may be considered as predisposing to pneumonia or affecting its course are listed in table 7. It is seen from this table that the cases of type II and type V pneumonia were closely similar with respect to the incidence of these conditions and their effect on the mortality. The findings with respect to these factors may be summarized briefly.

*Secondary Pneumonia*—Under this term are included those cases in which the onset of pneumonia occurred in the course of a severe acute illness or during an acute episode in a chronic illness. Postoperative pneumonia also was included. Congestive cardiac failure and acute infections, notably measles and pertussis in children, were the commonest primary conditions. Bronchopneumonia was predominantly secondary, whereas in only a small percentage of the cases was lobar pneumonia secondary to some other condition. The various primary conditions are noted in the table and in the footnotes.

*Alcoholism*—All patients from whom a history of alcoholic habits could be obtained were classified arbitrarily in three groups. The first group includes those who denied using alcoholic beverages or who rarely partook of small amounts, these are termed abstainers. The second group includes patients who regularly took small or moderate amounts, they are called mild or moderate chronic alcoholic patients. In the last category are considered those who were chronically addicted to the use of alcohol, who were acutely intoxicated or who had delirium tremens.

in the course of pneumonia. The progressively greater mortality in these three groups of patients is apparent from table 7.

*Acute Infection of the Respiratory Tract*—In about half the patients from whom a history was elicited in this regard some simple acute

TABLE 7—Incidence of Common Predisposing Factors in Cases of Pneumonia Due to Type II and Type V Pneumococci \*

		Type II Pneumonia								Type V Pneumonia							
		Lobar Pneumonia				Broncho pneumonia				Lobar Pneumonia				Broncho pneumonia			
		Recovered	Died	Mortality, per Cent	Incidence, per Cent	Recovered	Died	Mortality, per Cent	Incidence, per Cent	Recovered	Died	Mortality, per Cent	Incidence, per Cent	Recovered	Died	Mortality, per Cent	Incidence, per Cent
1	Primary conditions in cases of secondary pneumonia																
	Cardiac failure	1	4 <sup>a</sup>				4 <sup>b</sup>				3			1	5		
	Acute infection					1 <sup>c</sup>	2 <sup>d</sup>			1 <sup>e</sup>				2 <sup>f</sup>	5 <sup>g</sup>		
	Fracture		2 <sup>h</sup>			1 <sup>i</sup>								1 <sup>h</sup>			
	Cancer (terminal)						2 <sup>j</sup>									2 <sup>k</sup>	
	Operation	1 <sup>l</sup>				1 <sup>m</sup>				1 <sup>n</sup>						2 <sup>o</sup>	
	Other conditions	1 <sup>p</sup>	2 <sup>q</sup>				3 <sup>r</sup>			1 <sup>s</sup>	1 <sup>q</sup>			1 <sup>t</sup>	2 <sup>u</sup>		
	Total	3	8	73	5	3	11	79	93	3	4	57	7	5	16	76	64
2.	Alcoholism																
	Abstainers																
	Serum	29	6	17	50												
	No serum	32	12	28	48		2			21	8	27	47	3	7	70	58
	Mild to moderate, chronic																
	Serum	18	8	31	37												
	No serum	16	18	53	37	1	1			12	9	43	34	1	4	80	26
	Acute and/or delirium tremens																
	Serum	4	5	55	13												
	No serum	4	10	71	15		1			5	7	58	19	2	2	70	21
3	Antecedent acute infection of upper respiratory tract																
	Present																
	Serum	34	16	32	60	1	0										
	No serum	45	24	45	42	2	2	50	50	24	14	37	43	3	11	79	67
	Absent																
	Serum	23	10	30	40												
	No serum	61	34	44	58	0	4	100	50	29	22	43	57	3	4	71	33
4	Other conditions not directly related to onset of pneumonia																
	Chronic cardiac disease	2	7 <sup>a</sup>							1	3						
	Chronic pulmonary infections	7	6							4	3						
	Pregnancy	2									2					3	
	Diabetes	2 <sup>w</sup>								1	1					1	
	Antecedent otitis media	1								5							
	Acute urethritis	3								1							
	Others	4 <sup>x</sup>								2 <sup>y</sup>							
	Total	21	14	40	16	0				14	9	39	21	0	5	100	15

\* The significance of the superior letters used in the columns is as follows: a, indicates 1 with cirrhosis of liver, b, 1 with cirrhosis and asthma, c, measles, d, measles 1, scarlet fever and encephalitis 1, e, scarlet fever 1, pyelitis 1, f, scarlet fever, g, measles 1, pertussis 1, acute cholecystitis 1, h, ribs 1, skull 1, i, ribs, j, mouth 1, lung 1, k, both—cancer of lung with necrosis, l, peritonitis, m, bone flap for epilepsy, n, parturition, o, cholecysto-gastrostomy 1, ruptured appendix 1, p, hemoptysis (tuberculous), q, parturition, r, abscess of lung 1, cerebral thrombosis 1, coronary thrombosis 1, s, diabetic acidosis, t, cerebral thrombosis, u, acute psychosis with ingestion of iodine 1, pulmonary infarct 1, v, incidence is given as percentage of those with definite history, w, 1 with acute otitis media, x, bronchial asthma 2, convalescent from catarrhal jaundice 1, furunculosis 1, and y, secondary anemia, including 1 post partum.

infection of the upper respiratory tract, including the common cold, pharyngitis, grip, influenza and bronchitis, was present within two weeks preceding the onset of pneumonia. The mortality was the same among the patients with and those without such an antecedent infection.

*Other Conditions*—Under this heading in the table are listed focal infections and chronic diseases which were not considered to be directly related to the onset of pneumonia. Such conditions were present in 16 and 21 per cent, respectively, of the patients with primary lobar pneumonia due to type II and type V pneumococci. The mortality among these patients was the same as that for the entire group.

## CLINICAL FEATURES

It is of interest to compare some of the clinical characteristics of the pneumonia due to type II and that due to type V pneumococci.

TABLE 8—*Symptomatology*

	Cases of Type II Pneumonia*		Cases of Type V Pneumonia			
	Number	Per Cent†	Lobar Pneumonia		Bronchopneumonia	
			Number	Per Cent†	Number	Per Cent†
Mode of onset						
Sudden	157	83	86	84	19	63
Gradual	33	17	16	16	11	37
Initial symptom						
Chill	77	47	36	36	3	11
Pain in chest	52	32	34	34	11	39
Chill and pain in chest	15	9	7	7		
Chills, grip	3	2	9	9	6	22
Headache, weakness	8	5	4	4	1	4
Cough	3	2	3	3	5	18
Nausea, vomiting	3	2	3	3		
Bloody sputum	2	1	1	1		
Sore throat	1	0.6	1	1		
Abdominal pain			3	3	1	4
Epistaxis					1	4
Cardinal features						
Chill	151	77	68	73	8	37
Chest pain	178	92	94	90	18	82
Rusty sputum	118	77	50	63	7	47
All three	89	60	34	36	4	20
Only two	48	30	33	35	5	25
Only one	14	9	23	24	11	55
None	2	1	4	4	0	0

\* No reliable data were available in the cases of type II bronchopneumonia, because of the predominance of symptoms of other diseases.

† The percentage of incidence is figured on the basis of the cases in which a definite history was available on each point.

Some of the features in the histories of the patients and their frequency are listed in table 8. In the 15 patients with type II bronchopneumonia, in all of whom the condition was secondary, the symptomatology was related to the primary disease.

*Mode of Onset*—There was an abrupt onset in the great majority of cases, especially in the cases of lobar pneumonia. The commonest initial symptoms were chill and pleuritic pain, one or both of these symptoms ushering in the disease in 88 and 77 per cent, respectively, of the cases of lobar pneumonia due to type II and type V pneumococci and in 50 per cent of the cases of bronchopneumonia due to type V pneumococci.

*Cardinal Features*—Pleural pain was the most frequent symptom in all cases. A single chill and rusty or blood-tinged sputum, however, were more characteristic of the cases of lobar pneumonia. Either two or all three of these symptoms were present together in 90 per cent of the cases of type II and 71 per cent of the cases of type V lobar pneumonia, as compared with 45 per cent among cases of type V bronchopneumonia.

*Extent of the Pulmonary Involvement*—The relation of the site and the extent of the pulmonary lesion to the mortality is shown in table 9. The proportion of the patients with lobar pneumonia showing various

TABLE 9—Extent of Pulmonary Involvement

Lobes Involved		Type II Pneumonia						Type V Pneumonia					
		Serum			No serum			All Incl dence, per cent	Type V Pneumonia				
		Re cov ered	Died	Mor- tal ity, per cent	Re cov ered	Died	Mor- tal ity, per cent		Re cov ered	Died	Mor tal ity, per cent	Incl dence, per cent	
Lobar pneumonia													
Right	Lower	17	2		14	13		21	15	5		19	
	Upper and/or middle	7	2		12	0		14	7	8		14	
	Lower and middle	5	0		4	6		7	4	3		7	
	Upper and lower*	1	5		7	9		10	8	10†		17	
Left	Lower	24	4		18	9		25	19	7		24	
	Upper	0	0		2	2		2	0	1		1	
	Upper and lower	1	2		6	2		5	3	4		7	
	Total 1 lobe*	53	8	13	50	40	44	69	45	24	35	64	
Total 1 entire lung*		2	7	78	13	11	48	15	11	14	56	23	
Bilat- eral	2 lobes	4	8		3	9		11	3	7		9	
	3 lobes	0	0		2	2		2	1	0		1	
	4 or 5 lobes	0	4		1	2		3	1	1		2	
	Total bilateral	4	12	75	6	13	68	16	5	8	61	12	
Bronchopneumonia													
Mostly unilateral					1	3	75	27	5	8	61	39	
Bilateral					2	9	82	73	4	16	80	61	

\* With or without middle lobe

† Three patients also had bronchopneumonia on the left side

amounts of consolidation was closely similar among those with type II and those with type V pneumonia. In about two thirds of the patients with lobar pneumonia the consolidation was limited to a single lobe. As expected, the patients with the more extensive lesions showed a higher mortality than those with more limited involvement. It may be noted, in passing, that the only reduction in mortality following serum treatment occurred in cases in which the lesion was confined to one lobe.

*Duration of the Disease*—The duration of acute symptoms, including a temperature of 101 F and higher (by mouth), is given in table 10. It is worth noting that 44, or 76 per cent, of the patients with type II pneumonia who received serum treatment and who recovered were practically symptom-free by the end of the fifth day and 55, or 95 per



TABLE 10—Duration of the Disease

Day of Disease	Type II Lobar Pneumonia*				Type V Pneumonia			
	Serum		No Serum		Lobar Pneumonia		Bronchopneumonia	
	Recovered	Died	Recovered	Died	Recovered	Died	Recovered	Died
1	3	0	0	0	0	0	0	0
2	5	0	1	1	0	1	0	2
3	12	2	0	2	1	1	2	2
4	13	3	6	2	3	7	3	1
5	11	4	6	8	7	4	2	5
6	6	2	5	11	10	4	0	1
7	5	7	11	5	7	4	0	1
8	0	2	15	3	11	7	1	1
9	1	1	5	10	5	1	0	1
10	1	1	3	8	5	3	0	0
11	0	0	2	2	1	1	0	0
12	1	2	4	1	2	1	0	2
13	0	1	2	4	0	1	0	1
14	0	0	3	0	1	0	0	1
15-21	0	0	4	0	3	4	0	2
22+	0	3	1	1	0	4	1	1
?	0	0	1	6	5	3	0	3
Total	58	28	69†	64	61‡	46	9	24

\* The duration in type II bronchopneumonia could not be determined

† Crisis in 34 cases (49 per cent), lysis in 35 cases (51 per cent)

‡ Crisis in 27 cases (44 per cent), lysis in 34 cases (56 per cent)

TABLE 11—Complications (Diagnosed During Life) \*

Complications	Type II Pneumonia				All 219 Cases	Type V Pneumonia, 140 Cases			
	Serum (86 Cases)		No Serum (133 Cases)			Incidence, per Cent	Recover- ed	Died	Incidence, per Cent
	Recover- ed	Died	Recover- ed	Died					
Empyema	3 <sup>a</sup>		3 <sup>b</sup>	2	3.6	9 <sup>c</sup>	6 <sup>d</sup>	10.7	
Meningitis				4 <sup>e</sup>	1.8		2	1.4	
Pericarditis							1	0.7	
Otitis media	2 <sup>f</sup>		1 <sup>f</sup>	1	1.8	3 <sup>g</sup>		2.1	
Sterile pleural effusion	3		4 <sup>h</sup>	1	3.6	2 <sup>i</sup>	1	2.1	
Acute tonsillitis	2 <sup>h</sup>		1		1.4	3		2.1	
Pyelitis	1				0.5			0.7	
Conjunctivitis			1		0.5	1			
Acute nephritis						2		1.4	
Subcutaneous abscesses	1 <sup>j</sup>		1 <sup>k</sup>	1	1.4				
Miscarriage	1		1		0.9		1	0.7	
Jaundice	4	2	5	2	5.6	1	2	2.1	
Furunculosis			1 <sup>l</sup>		0.4				
Granulopenia				1	0.4				
Meningismus							1	0.7	
Air embolus							1	0.7	
Thrombophlebitis						1		0.7	
Auricular fibrillation		2	1	8 <sup>m</sup>	5.0		2 <sup>n</sup>	1.4	
Delirium tremens		3	2	7 <sup>m</sup>	5.5	1	2 <sup>m</sup>	2.4	
Atelectasis (roentgen diagnosis)			2	3	2.3	2	4	4.3	
Extensions	1 <sup>o</sup>	4 <sup>o</sup>	6	5	7.3	6	12 <sup>p</sup>	12.9	

\* The significance of the superior letters used in these columns is as follows: a indicates 1 with Str. haemolyticus on culture, and otitis media; b, bronchopneumonia 1, 1 also had pneumococcal conjunctivitis; c, bronchopneumonia with otitis media 1, acute nephritis and otitis media 1, Str. haemolyticus on culture 1, d, bronchopneumonia 2, pericarditis 1, e, bronchopneumonia 1, otitis media 1, f, Str. haemolyticus and Staph. aureus cultured from 1, g, jaundice 1, h, pyelitis 1, i, acute tonsillitis 1, j, miscarriage, k, no growth on culture, l, Staph. aureus, m, bronchopneumonia 1 n, both bronchopneumonia, o, all occurred in 1932-1935,<sup>23a</sup> and p, bronchopneumonia 4

cent, were relieved after the seventh day of illness. Compared with these figures, only 19 per cent of the patients with type II pneumonia and 18 per cent of those with type V lobar pneumonia who did not receive serum treatment were free from fever and symptoms of acute infection by the end of the fifth day, and 42 and 46 per cent, respectively, were relieved after the seventh day.

TABLE 12—*Bacteremia in Pneumonia Due to Type II and Type V Pneumococci, Incidence, Mortality and Relation to Age*

	Patients with Bacteremia					Patients Showing Sterile Blood Cultures				
	Type II*			Type V		Type II			Type V	
	Serum	No Serum	All	Lobar pneumonia	Broncho pneumonia	Serum	No Serum	All	Lobar pneumonia	Broncho pneumonia
Number of cases	30	53	83	31	11	47	39	86	48	12
Per cent incidence†	39	58	49	40	48	61	42	51	60	52
Died	19	38	57	27	11	6	10	16	10	8
Per cent mortality	63	72	69	84	100	13	26	19	21	75
19 years or less										
Number	2	0	2	1	3†	9	9	18	8	1†
Per cent of age group	18	0	10	11	75	82	100	90	89	25
Died	1	0	1	0	3	0	0	0	1	1
Per cent mortality	50		50	0	100	0	0	0	13	100
20-39 years										
Number	14	17	31	10	3	24	18	42	23	2
Per cent of age group	37	49	42	30	60	63	51	58	70	40
Died	9	8	17	7	3	2	5	7	2	0
Per cent mortality	64	47	55	70	100	8	28	17	9	0
40-59 years										
Number	11	25	36	11	3	14	10	24	15	5
Per cent of age group	44	71	60	42	37	56	29	40	58	63
Died	7	21	28	11	3	4	4	8	6	4
Per cent mortality	64	84	78	100	100	29	40	33	40	80
60 years and older										
Number	3	11	14	10	2	0	2	2	2	4
Per cent of age group	100	85	87	83	33	0	15	13	17	67
Died	2	9	11	9	2	0	1	1	1	3
Per cent mortality	67	82	79	90	100		50	50	50	75

\* Of the patients with bronchopneumonia 4 (aged 1, 50, 67 and 75 years) had bacteremia and 5 (aged 2, 5, 35, 50 and 56 years) showed sterile cultures, an incidence of 44 per cent for bacteremia.

† All under 1 year of age.

‡ Per cent of cases in which blood cultures were made.

*Complications*—The complications noted during the course of the disease or during convalescence are listed in table 11. Empyema and extension of the pulmonary lesion were relatively more frequent among the patients with type V pneumonia, whereas delirium tremens and auricular fibrillation were more frequent among those with type II pneumonia.

TABLE 13—Course of Bacteremia in Relation to Outcome

Case	Se rum, Day*	Days After Onset													
		2	3	4	5	6	7	8	9	10	11	12	13	14+	
Type II, serum treatment															
1	4		B	1, 0	0	0, L	0								
2†	3		3	0	SA	SA								SH	
3	2	362	B	0	0, L	0			0						
4	2	+	400, 88, 200, B	D											
5	3		1,000												
6	3		B	0, C											
7	4		B	0	0, 0	0, D									
8	4		+	+	+	0	D								
9	13											91	D	0	
10	4		2,000	4,000	9, D	+									
11	3	+	15	0		0	273	1, D	0						
12	2	0				+				0	L				
13	2	+	C	0											
14	2	0	+	0		+	D								
15	2	+	0, I	0			D								
16	9	+		0		0		+	0		+		D		
17	3		+	+, D	+										
18	2	+	0		0		D								
19	7					+			D, +						
20	3		+			+									
21	4		+		0			0			L				
22	4			+	D	+									
23	2		+		0	0			+		+		D	0	
24	2	0		+	D	+									
Type II, no serum treatment															
1				250	17			0	C					0	
2			4, 0	600	2,000	D									
3					5	1			1		1,000	1,000, D			
4							700	700		D					
5		1,600	10,000, D												
6					+	+, D									
7				600		1,200	D								
8		0	0	0	0	2	D								
9		0	B	0	0		0				L				
10								3, 100, D							
11				B		0		0							
12							+	+							
13								+							
14															
15				380	17,000	D									0, L
16							+	+, D							
17				0	D, +										
18					+, D	0									
19					+		+, D	+							
20						24	30	6	4	D	0				
21							+	D							
22					+	0	D	0							
23		+	+			0	L	0							
24					+	0	0	0, C							
25				0			+			D					
26						+	D	+							
27									+	+	+	+, D	+		
28							+		+	D					
29						0				+, D	0				
Type V															
1				16	200, D										
2†							3	5	0	SH	D				
3					0								+	D	
4		2	4		200	490	D, +								
5					+	50									
6							5	1,700§	0	0		L			
7			+			+	D	+							
8								+			+, D	0			
9							0	D	+						
10					+			0	C						
11					+	+	D	+							
12															
13				+	D	+									
14															
15				+				0	L		D	+			
16						+	+								
17				+	D	+									
18						+									
19			0		0		D	+							
20								+, D	+						

\* First day of serum treatment

† Empyema (*Str. haemolyticus*) and otitis media (*Staph. aureus* also), recovered

‡ Treated with type II antibodies

§ Retained placenta removed on this day

D indicates died, L, lysis; C, crisis, SA, *Staph. aureus*, SH, *str. haemolyticus*, +, pneumococci cultured from broth, no counts made, and B, pneumococci in broth culture, plates sterile. The numbers represent colonies per cubic centimeter of blood. Cultures that were made after death were made from heart blood at autopsy.

TABLE 14—*Resume of the Autopsy Observations in Cases of Pneumonia Due to Type II and Type V Pneumococci*

	Type II Pneumonia		Type V Pneumonia	
	Lobar Pneumonia	Broncho pneumonia	Lobar Pneumonia	Broncho pneumonia
Number of cases	38 <sup>a</sup>	10	22 <sup>b</sup>	20
Pulmonary involvement				
1 lobe	8	2	6	4
2 lobes	13	3	8	2
3 lobes	13	2	8 <sup>b</sup>	3
4 lobes	3	0	0	0
5 lobes	1	3	0	11
Unilateral	24	3	20 <sup>b</sup>	7
Bilateral	14	7	2	13
Purulent pneumococcal complications				
Empyema <sup>c</sup>	7 <sup>f</sup>	2	7 <sup>g</sup>	4 <sup>h</sup>
Pericarditis	3	1	5	0
Vegetative endocarditis	5	1	1	0
Meningitis	3	1	0	0
Pulmonary abscesses <sup>d</sup>	8 <sup>r</sup>	1	4 <sup>g</sup>	4
Bronchitis	15	4	15	10
Tracheitis	6	3	8	4
Skin abscess <sup>e</sup>	3	1	0	3
Otitis media, mastoiditis	1	0	0	2
Peritonitis	0	0	2	3
Slimy pneumonic exudate	4	0	0	0
Nonseptic complications				
Sterile pleural effusion <sup>c</sup> (100 cc or more)	7 <sup>g</sup>	2 <sup>f</sup>	8 <sup>f</sup>	3 <sup>g</sup>
Fibrinous pleuritis <sup>c</sup> <sup>f</sup>	36 <sup>d</sup>	4 <sup>f</sup>	18 <sup>g</sup>	13 <sup>g</sup>
Atelectasis	2	0	2	4
Organization of lung	6	1	3	0
Infarcts, thromboses	4 <sup>e</sup>	3 <sup>h</sup>	3 <sup>f</sup>	2 <sup>f</sup>
Acute hepatic necrosis	5	2	1	1
Jaundice	3 <sup>h</sup>	1	2	1
Acute cardiac dilatation <sup>c</sup> <sup>u</sup>	7 <sup>g</sup>	3	4 <sup>f</sup>	3
Ascites	2 <sup>h</sup>	2 <sup>f</sup>	0	2
Purpura	0	0	0	0
Acute tubular nephritis	1	0	0	0
Other complicating conditions (excluding degenerative diseases)				
Fibrous pleural adhesions (old) <sup>c</sup>	28 <sup>h</sup>	3 <sup>g</sup>	11 <sup>g</sup>	12 <sup>g</sup>
Chronic pulmonary disease	7 <sup>m</sup>	3 <sup>h</sup>	4 <sup>o</sup>	6 <sup>p</sup>
Chronic endocarditis	3	3	3	1 <sup>q</sup>
Infection of urinary tract	6	1	5	1
Ulcers (gastro intestinal)	2	0	0	1
Cirrhosis of liver	7	1	1	1
Miscellaneous	0	0	5 <sup>r</sup>	1 <sup>q</sup>
Bacteriologic data				
Heart blood positive	21	3	13	8
negative	10	7	4	6
Str haemolyticus	1	0	1	1
Mixed infections <sup>t</sup>	6	3	3	3

\* The significance of the superior letters used in the columns is as follows: a, indicates including 1 with lobar pneumonia (right) and bronchopneumonia (left); b, including 3 with lobar pneumonia (right) and bronchopneumonia (left); c, the number with this complication on both sides is indicated by the superior numbers (in 3 of the cases of unilateral empyema [type V] there was a contralateral sterile pleural effusion); d, number of cases of parenchymatous necrosis noted only microscopically is indicated by superior number; e, including decubitus ulcers; f, including empyema; g, lung, left ventricle, kidney and spleen 1, right ventricle 1, kidney 1, spleen 1, h, lung, right ventricle and spleen 1, coronary artery 1, cerebral artery 1; i, splenic vein 1, coronary artery 1, pelvic veins 1, j, lung and iliac veins 1, lung 1, k, 2 with cirrhosis of liver, l, 1 with cirrhosis of liver; m, emphysema 3; bronchiectasis 2; chronic bronchitis 1; bronchiogenic carcinoma 1; n, emphysema 3; o, emphysema 3; bronchiectasis 1; p, bronchiogenic carcinoma 1; metastatic carcinoma (breast) 1; bronchiectasis 2; emphysema 2; q, congenital heart disease; r, chronic passive congestion 2; salpingitis 1; hypertensive heart disease 1; abdominal hernia, incarcerated 1; s, subarachnoid hemorrhages; t, see tables 3 and 4; and u, dilatation was left sided in 1 case of type II bronchopneumonia and in 1 case of type V lobar pneumonia, other unilateral dilatations were right sided.

## BACTEREMIA

The incidence of bacteremia and the percentage of mortality among patients with type II and type V pneumonia are recorded in table 12. Pneumococci were cultured from the blood stream in about half the cases of each type. In the 73 fatal cases of type II pneumonia in which blood cultures were made, 57, or 78 per cent, of the patients were bacteremic, but only 26, or 27 per cent, of the 96 who recovered showed positive results of blood culture. Of the patients with type V pneumonia, 38, or 68 per cent, of those who died and 5, or 11 per cent, of the 47 who recovered showed positive results of blood culture. Thus, bacteremia was three or more times as frequent among the patients who died as among those who survived. The high incidence of bacteremia in cases of both types may have an important bearing on the high mortality in these cases.<sup>25</sup>

There is an increasing incidence of bacteremia with advancing age. This may be related to the natural immune processes which become less effective in older persons. The cases of bronchopneumonia in which blood cultures were made are so few that deductions cannot be drawn. The irregular mortality and incidence of bacteremia with respect to the different age groups is consistent with the secondary character of these atypical cases. This indicates that the primary disease or other factors combined with the factors of immunity<sup>26</sup> bring about the fatal outcome.

The course of bacteremia in patients from whom multiple blood cultures were made is shown in table 13. The effect of serum therapy on bacteremia is discussed elsewhere.<sup>23</sup> The largest number of colonies per cubic centimeter of blood cultured from patients who recovered were 1,700 from a patient with type V pneumonia, 250 from a patient who did not receive serum treatment and 362 from a patient with type II pneumonia who received serum treatment. Much larger numbers were encountered in fatal cases shortly before death. It should be noted that death may occur in cases of bacteremia even after pneumococci can no longer be cultured from the blood stream. Transient and recurrent bacteremia also was encountered in the fatal cases.

## AUTOPSY OBSERVATIONS

*Focal and Other Infections*—Autopsies were performed on 53 patients with type II infections and on 46 patients with type V pneumococcal infection. The protocols, which included histologic studies in each instance, were reviewed in every case. In 5 (9.4 per cent) of

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25 Bullowa, J. G. M., and Wilcox, C. Incidence of Bacteremia in the Pneumonias and Its Relation to Mortality, *Arch Int Med* **55** 558 (April) 1935. Cecil and Plummer.<sup>12b</sup>

26 Sutcliffe, W. D., and Finland, M. Antipneumococcal Immunity Reactions in Individuals of Different Ages, *J Exper Med* **55** 837, 1932.

the patients with type II infection and in 4 (87 per cent) of those with type V infection, no pneumonia was found which could be attributed to the pneumococcus. Sepsis (pneumococci in the culture of the heart blood) without a demonstrable focus was present in 3 of the cases of nonpneumonic type II infection, the fourth patient had pneumococcal meningitis and sepsis, and the fifth had otitis media due to type II pneumococci and meningitis due to *Staphylococcus aureus*. In 2 cases of type V nonpneumonic infection pneumococci were cultured from purulent otitic or mastoid exudate, but beta hemolytic streptococci were cultured from material from the blood and lungs in both cases and from material from the meninges in 1 case. The other 2 patients had focal purulent complications of bronchiogenic carcinoma, the type V pneumococci being cultured along with other organisms, from an infected hydrothorax in one and from a bronchiectatic abscess in the other.

The data with regard to the cases of pneumonia are listed in table 14. Some of the features are briefly mentioned here.

*Character and Extent of the Pulmonary Lesion*—Bronchopneumonia was noted more frequently at autopsy than clinically. The pulmonary lesion was atypical in 10, or 21 per cent, of the cases of type II infection and in 20, or 47 per cent, of the cases of type V infection. In addition, 1 of the patients with type II infection and 3 of the patients with type V infection had lobar pneumonia involving the entire right lung and diffuse bronchopneumonia of the left lung. The greater incidence of bronchopneumonia is attributable to the fact that, particularly in the cases of type II infection, either the pulmonary lesion or its pneumococcal etiology or both were often first recognized at the time of autopsy. Among the patients with lobar pneumonia, bilateral involvement was relatively more frequent in the type II infection than in the type V infection, but the lesions were confined to one lung in most of the cases of either type.

*Purulent and Other Complications*—The relatively high incidence of empyema (26 per cent), pericarditis (12 per cent) and peritonitis (12 per cent) among the patients with type V pneumonia and of endocarditis (12.5 per cent) and meningitis (8 per cent) complicating type II pneumonia is worth noting. The cases of peritonitis (3 in males and 2 in females) were all in adults between 28 and 48 years old. It is also of interest, because of the possible bearing on the clinical diagnosis, to note the large proportion of cases of tracheobronchitis. In most instances the bronchitis involved, in addition to the consolidated regions, lobes in which the parenchyma was not affected. Slimy pneumonic exudate, usually considered characteristic of infection with type III

pneumococcus or with Friedlander's bacillus, was noted in 4 cases of lobar pneumonia due to type II pneumococci

Among the pleural complications, fibrinous pleuritis and sterile effusions were the most frequent. The presence of old fibrous pleural adhesions in more than two thirds of all the cases is of interest in view of the recent interest in pneumothorax therapy

*Bacteriologic Observations*—In all but 9 of the cases autopsy was performed within twenty-four hours after death. Type II or type V pneumococci in pure culture were recovered from the lung and other foci in almost every case, even when the autopsy was performed as long as nine days post mortem. These organisms were recovered also from the blood in the majority of instances. In only 3 cases were other organisms (beta hemolytic streptococci) cultured from this source. The frequency with which other organisms were cultured from all sources at autopsy is noted in table 14, and their sources are listed in table 4.

#### COMMENT

The purpose of this presentation has been primarily descriptive. It is part of a study designed to evaluate the significance of different types of pneumococci, particularly those recently differentiated from the old group IV, with respect to the host which they invade and the disease which they produce. No effort has been made, however, to include all aspects of the symptomatology, the physical signs and the results of therapy. There is presented here a base line which may be used, on the one hand, to compare the diseases caused by these two types of pneumococci with those resulting from other bacterial agents and, on the other hand, to evaluate the results of various general or specific therapeutic agents in cases of pneumonia due to these types. It may serve also to give a comparison of the characteristics of the disease caused by the same organisms in different localities.

The greatest significance of the recognition of the etiologic agent in cases of pneumonia, as in cases of other infections, is with respect to specific therapy. From this point of view the importance of distinguishing type V from type II pneumococci has been pointed out elsewhere<sup>27</sup>. We have here compared the pathogenicity for man of these two types of pneumococci. With respect to their close association with pulmonary infection, these two types are closely similar. They are comparable, in this respect, with type I and stand out in contrast to the type III pneumococci.

Within the lungs type V pneumococci may be said to produce, in general, a similar but less typical pulmonary lesion than is usually caused by type II pneumococci. Type V pneumonia is more often

<sup>27</sup> Cooper and others<sup>1b</sup> Finland and Winkler<sup>5b</sup>

secondary to a serious disease. In a larger proportion of cases type V pneumonia is atypical or is so-called bronchopneumonia, but the patients with type V bronchopneumonia exhibit a clinical picture more like that of typical lobar pneumonia than do the patients with type II bronchopneumonia. The gradation from the most typical to the most atypical pneumonia would be as follows: type II lobar pneumonia, type V lobar pneumonia, type V bronchopneumonia and, lastly, type II bronchopneumonia. With respect to the commonest of the other types, the clinical picture of type V infections seems to occupy a middle ground between type I and type II infections, on the one hand, and the more atypical type III and type VIII infections," on the other hand.

#### SUMMARY

Both type II and type V pneumococci were found to be associated with pneumonia with great regularity. In a small percentage of cases these organisms were isolated from lesions due to focal infection, or they were present in the sputum or nasopharynx without relation to disease. Various characteristics of the infections, particularly pneumonia, caused by these two types of pneumococci are recorded.

Like pneumonia due to type II pneumococci, the cases produced by type V pneumococci are usually lobar in character. Atypical pneumonia or bronchopneumonia, however, is far more frequent in the cases of type V infection. Lobar pneumonia due to type V pneumococci may be less characteristic than the condition due to type II pneumococci.



# NONBACTERIAL THROMBOTIC ENDOCARDITIS

## CLASSIFICATION AND GENERAL DESCRIPTION

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According to Libman,<sup>1</sup> endocarditis may be classified as rheumatic, syphilitic, acute bacterial, subacute bacterial and indeterminate. The indeterminate group includes a number of heterogeneous types characterized by nonbacterial, verrucous endocardial deposits, which cannot clearly be placed under the preceding headings. Certain forms in this indeterminate group, occurring toward the end of chronic diseases like carcinoma, leukemia or nephritis, were called terminal endocarditis. These corresponded to the cachectic endocarditis mentioned by Harbitz.<sup>2</sup> In 1923 Libman and Sacks<sup>3</sup> further segregated from the instances of the indeterminate group four cases in which the clinical and pathologic features were sufficiently uniform to constitute a definite syndrome. Because of the peculiar appearance of the gross endocardial lesions in this group of cases, the condition was termed "atypical verrucous endocarditis." In 1932 one of us (L. G.)<sup>4</sup> made a detailed study of the pathologic changes of the hearts of eleven patients with this disease. In the course of this study a number of instances of a type of indeterminate endocarditis were encountered in which the condition differed from the "atypical verrucous" form and which required further study and classification. These and certain additional cases in which the condition was similar form the basis of the present report.

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From the Medical Services and the Laboratories of the Mount Sinai Hospital.  
Aided by grants from the Lucius N. Littauer Fund and the Walter W. Naumburg Fund.

1 Libman, E. Characterization of Various Forms of Endocarditis, *J. A. M. A.* **80** 813-818 (March 24) 1923.

2 Harbitz, F. *Deutsche med. Wchnschr.* **25** 121-124, 1899.

3 Libman, E., and Sacks, B. A Hitherto Undescribed Form of Valvular and Mural Endocarditis, *Arch. Int. Med.* **33** 701-737 (June) 1924.

4 Gross, Louis. The Heart in Atypical Verrucous Endocarditis (Libman-Sacks), in *Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues*, New York, International Press, 1932, vol. 2, pp. 527-550.

## NOSOLOGY

The early division of endocarditis into verrucous and ulcerative forms was discarded because of a lack of correlation with etiologic and clinical features. Current classifications are based in part on etiologic grounds but chiefly on groups of clinical features which apparently constitute definite homogeneous syndromes. In general, endocarditis may be divided into three major types, bacterial, nonbacterial and syphilitic (table 1). The last mentioned may be listed as a major type, even though it occurs infrequently, with the reservation that it is seldom, if ever, a primary endocarditis, since it generally produces only a commissural and basal valvulitis. In bacterial endocarditis, organisms are almost invariably found in the vegetations and in the circulating blood.<sup>5</sup> In contradistinction to this, bacteria are not found in significant numbers in the vegetations at necropsy in the nonbacterial types of

TABLE 1—*Classification of Endocarditis to Show Position of Nonbacterial Thrombotic Endocarditis*

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1	Bacterial endocarditis (bacteria cultivated consistently from the blood intra vitam and from the vegetations post mortem, also rare cases of tuberculous endocarditis)
A	Acute bacterial endocarditis (pyogenic organisms)
B	Subacute bacterial endocarditis (nonhemolytic streptococci, gonococci, influenza bacilli, etc.)
	1 With bacteremia
	2 In the bacteria free stage
2	Nonbacterial endocarditis (may be due to bacteria or other infectious agents but thus far not proved)
A	Rheumatic endocarditis
B	Indeterminate endocarditis
	1 Atypical verrucous endocarditis (Libman Sacks)
	2 Nonbacterial thrombotic endocarditis (described and classified in this report, includes many of the conditions called terminal or cachectic endocarditis)
3	Syphilitic endocarditis

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endocarditis, nor can organisms be cultured from the blood stream during life. It must be borne in mind, however, that this may be due to the inadequacy of the methods available, and in this sense the term nonbacterial is a misnomer, as newer methods may disclose a bacterial or other etiology in some of these cases.

The major type of nonbacterial endocarditis comprises two subtypes—rheumatic and indeterminate endocarditis. The true nature of these is as yet undetermined. However, the word “undetermined” should not be confused with the connotation implied by Libman’s term “indeterminate.” With him, we use the term to indicate that the true position of a given condition relative to other diseases is as yet unclear, or indeterminate, from the point of view of both clinical and pathologic diagnosis. From this definition it is obvious that rheumatic endocarditis does not properly belong to the indeterminate category, since this

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5 In the rare cases of tuberculous endocarditis reported the clinical picture of bacterial endocarditis is not present (Dressler, W. Zur Kenntnis der Tuberkulose der Herzklappen, Frankfurt Ztschr f Path **26** 401-405, 1921-1922).

disease has a definite clinical picture and certain distinctive histologic features (for example, the specific Aschoff body) which sharply distinguish it from other lesions. It is therefore listed as a separate subtype in the nonbacterial classification.

The remaining forms of nonbacterial endocarditis form a second subtype and constitute the indeterminate type of endocarditis. These include atypical verrucous endocarditis (Libman-Sacks) as well as other conditions which we shall classify and describe in this report as "nonbacterial thrombotic endocarditis." In spite of the fact that atypical verrucous endocarditis has certain clinical and pathologic features which seem to entitle it to separate classification as a subtype of nonbacterial endocarditis, as in the case of rheumatic endocarditis, Libman expressed the belief that knowledge of this disease is as yet so fragmentary and its relation to other conditions is so uncertain that it is better to continue to consider it a division under the indeterminate subtype.

There remain therefore in the indeterminate classification a number of forms which differ clinically and pathologically from those mentioned. These apparently do not represent a homogeneous syndrome like rheumatic or atypical verrucous endocarditis but comprise a variety of conditions. In all of these forms nonbacterial, nonreactive or mildly reactive thrombotic vegetations are present on the cardiac valves. In many cases the thrombotic deposits are secondarily engrafted on a damaged valve, the damage usually being due to a completely healed rheumatic lesion. Such healed rheumatic valvulitis belongs in type VI of our classification (inactive or healed rheumatic fever).<sup>6</sup> Thus, these conditions may be classified under two different categories—type VI rheumatic fever (inactive or healed), because of the underlying rheumatic process, and nonbacterial thrombotic endocarditis, because of the secondarily engrafted thrombotic process. This dual classification is strictly analogous to the occurrence of bacterial vegetations in subacute bacterial endocarditis on a rheumatic process.

In choosing a title for this subdivision we sought some feature which occurred in all cases. As was mentioned before, we found this to be the presence of nonbacterial thrombotic vegetations on the valves. We are therefore employing the term nonbacterial thrombotic endocarditis as a general descriptive heading, although we are well aware of the shortcomings of such a name. We have deliberately avoided the use of the term thrombo-endocarditis, which was originally employed by Ziegler.<sup>7</sup> It was his belief that in a large number of instances

6 Gross, Louis, and Friedberg, C. K. Lesions of the Cardiac Valve Rings in Rheumatic Fever, *Am J Path* **12** 469 (July) 1936.

7 Ziegler. *Verhandl d deutsch Kong f inn Med* **7** 339-343, 1888.

vegetations occurred not as a result of inflammatory disease but as marantic thrombi similar to thrombi in blood vessels. More recently, when the term thrombo-endocarditis is employed, it refers to a general grouping which includes rheumatic endocarditis as well as the conditions under discussion. It seems, therefore, that to attempt to employ the term in its original sense would lead to confusion. The use of the term simple endocarditis as suggested by Koniger,<sup>8</sup> or simple thrombo-endocarditis, contributes nothing to the descriptive value of the title.

Since the individual types of nonbacterial thrombotic endocarditis cannot be distinguished by the histologic appearance of the lesion, classification will be based on their association with some significant clinical or clinicopathologic condition (table 2). When a more definite

TABLE 2—*Classification of Forty-Seven Cases of Nonbacterial Thrombotic Endocarditis*

1 Cases in which the condition was associated with thrombocytopenic purpura, etc.	3
2 Cases in which the condition was associated with peculiar arthritis and involvement of serous membranes (in one case with periarteritis nodosa)	4
3 Cases of cachectic and infectious disease associated with chronically deformed valves, usually rheumatic	32
Carcinomatosis	7
Glomerulonephritis (in one case associated with periarteritis nodosa)	5
Pulmonary emphysema and fibrosis	3
Rheumatic cardiovascular disease with congestive failure	2
Uremia	2
Lobar pneumonia	2
Leukemia	2
Pseudoleukemia	1
Miliary tuberculosis	1
Chronic osteomyelitis	1
Purulent mediastinitis	1
Subarachnoid hemorrhage	1
Cirrhosis of the liver	1
Fibrinopurulent peritonitis	3
4 Cases of cachectic diseases with verrucae on relatively normal valves	5
Carcinomatosis	4
Uremia	1
5 Unclassified	3

etiology is discovered, these descriptions and designations may be amplified.

In discussing the cases of terminal endocarditis which we include as instances of nonbacterial thrombotic endocarditis, Libman<sup>1</sup> pointed out that this group required renewed investigation. It was in the light of that suggestion that this study was conducted. We shall describe the gross and microscopic appearance of the various types of valvular lesions encountered and shall segregate the clinical syndromes with which nonbacterial thrombotic endocarditis is associated. In this connection we have tried to ascertain whether this type of endocarditis occurs merely as an accidental finding in commonly encountered diseases or whether it is present as part of definite syndromes comparable to

8 Koniger, H. *Arch. d. path. Inst. zu Leipzig* 1:1-162, 1903.

rheumatic or atypical verrucous endocarditis. Finally, we have endeavored to ascertain whether any particular factors throw light on the etiology of pathogenesis of the endocardial lesions.

#### MATERIAL AND METHODS

This study is based on patients who came to autopsy in the Mount Sinai Hospital in the twenty years preceding the time of writing. During this period the diagnosis of indeterminate, terminal or nonbacterial thrombotic endocarditis was made at necropsy in about one hundred and fifty cases. For various reasons the majority of autopsy reports could not be used. In many instances more detailed investigation led to a revision of the diagnosis, as it seemed probable or certain that the vegetations indicated active rheumatic or bacterial endocarditis. In an even larger number, while the evidence of rheumatic or of healed bacterial endocarditis was uncertain, such possibilities could not be excluded and the cases were omitted. We have limited ourselves, therefore, to the cases in which the verrucae were of recent origin, because in these the possibility of confusion with the healed stages of known forms of endocarditis is less likely. In many cases in which the valves showed knobs or nodules which were completely organized or hyalinized, we could not be certain whether such lesions were of inflammatory or of thrombotic origin or were the result of degeneration or tension. Such cases were not included. When we had limited our material in this manner, there remained forty-seven cases in which the condition fulfilled our criteria of nonbacterial thrombotic endocarditis. A study of these forty-seven cases forms the basis of this report.

The specimens were prepared as described previously in other publications,<sup>4</sup> and blocks were cut according to the standardized method of Gross, Antopol and Sacks.<sup>9</sup>

#### PATHOLOGIC CHANGES IN NONBACTERIAL THROMBOTIC ENDOCARDITIS

The following description presents the cardiac pathologic picture of nonbacterial thrombotic endocarditis in general. Special points will be considered in connection with the several subdivisions according to associated clinical diseases.

*Valvular Lesions*—*Macroscopic Features*. The most striking and characteristic feature was the presence of valvular vegetations, which were occasionally of unusual appearance but were not specific in form, size or location. They were frequently larger than those associated

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<sup>9</sup> Gross, Louis, Antopol, W., and Sacks, B. Standardized Procedure Suggested for Microscopic Studies on the Heart, with Observations on Rheumatic Hearts, *Arch. Path.* **10** 840-852 (Dec.) 1930.

with rheumatic endocarditis. They never involved the mural endocardium or the pockets of valves as do those associated with atypical verrucous endocarditis.

The most common type of verrucous lesions was the pyramidal ridge (Gross<sup>4</sup>). This lesion consisted of narrow discontinuous bands of yellowish, confluent deposits, superimposed on and firmly attached to a ridgelike thickening of the closure line of a generally thickened valve. It was found in more than half the cases, without special predilection for any particular type. Frequently irregular clusters or rows of discrete or confluent pinhead-sized grayish or yellow verrucae, occasionally



Fig 1—Nonbacterial thrombotic endocarditis of the right aortic cusp associated with purulent peritonitis. The verrucae resemble the type seen in rheumatic endocarditis.

friable, were superimposed on the ridgelike thickenings, giving a crown-like effect (fig 1).

More distinctive and next in frequency were the conglomerate, or massive thrombotic, vegetations (figs 2, 3 and 4). They were the size of a pea, sometimes larger, grayish-pink or tawny, of granular appearance and usually friable, sometimes they had the appearance of bacterial vegetations. A rather characteristic feature was the tendency to involve the commissures of the mitral valve or of the pulmonic and aortic cusps, more rarely the nodulus Arantii of the aortic valve (fig 4). In a few cases the vegetations took the form of knobbed stalks or pendulous tabs (fig 5).



Fig 2—Nonbacterial thrombotic endocarditis of the mitral cusps associated with fibrinopurulent peritonitis. The lesion is of the massive conglomerate type.



Fig 3—Nonbacterial thrombotic endocarditis of the mitral cusps associated with carcinoma of the colon. The arrows point to massive conglomerate lesions, which have undergone considerable organization. Note the thickening of the valve leaflets and the chordae tendineae, evidences of a previous rheumatic infection.



Fig 4—Nonbacterial thrombotic endocarditis of the aortic cusps associated with carcinoma of the colon. Note the localization of the verrucae on the thickened corpora Arantii.



Fig 5—Nonbacterial thrombotic endocarditis associated with miliary tuberculosis. The arrow points to a lesion of the polypoid type. Note the fusion and thickening of the chordae tendineae, evidences of a former rheumatic infection.



The mitral valve showed thrombotic vegetations in all cases but one. The aortic valve was affected eleven times, the tricuspid valve five times and the pulmonic valve twice. There was little or no tendency for these vegetations to cause valvular deformities. Such deformities, when present, were obviously the result of old and inactive rheumatic endocarditis. In twenty-nine cases there was a significant thickening of the mitral valve, and in four or five cases there was thickening of the aortic and tricuspid valves. Mitral stenosis was present in nine cases, aortic stenosis twice and aortic insufficiency once. The nature of such

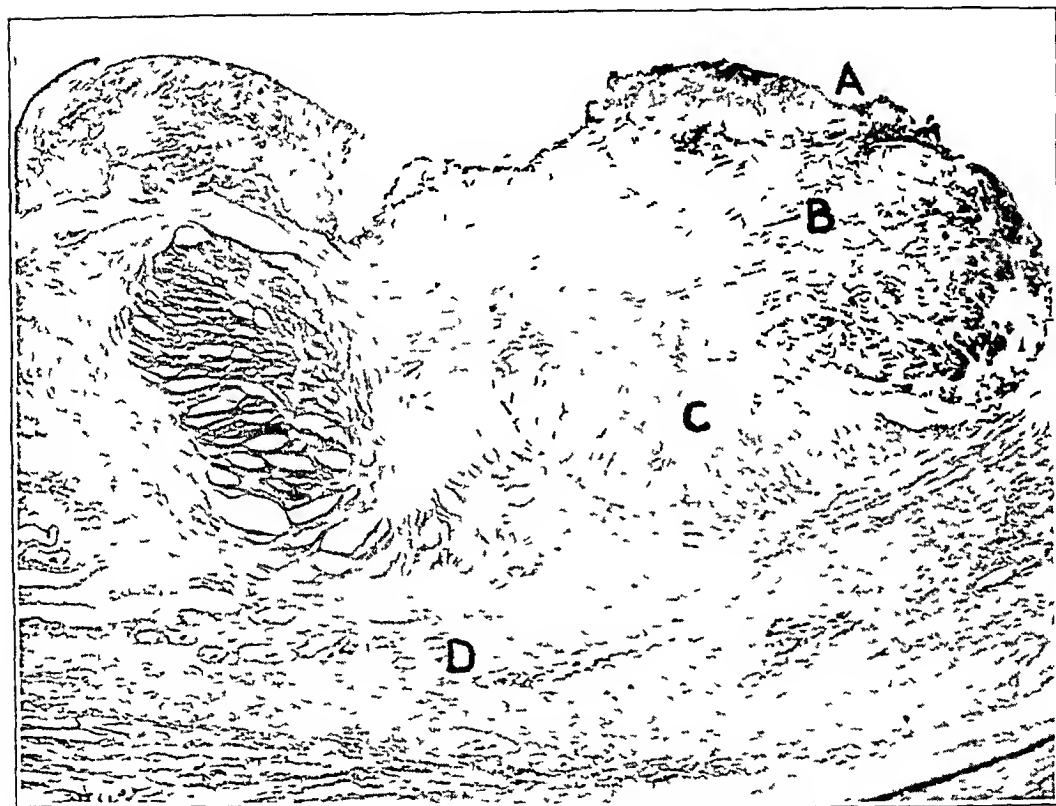


Fig 6—Nonbacterial thrombotic endocarditis of the mitral valve. Low power photomicrograph of a section stained with hematoxylin and eosin. *A*, a remnant of blood platelet thrombus superimposed on and fused with *B*, eosinophilic change of an organized valve lesion. *C*, hyalinization of an organized valve lesion. *D*, vascularization and thickening of an auricularis layer, probably evidence of old rheumatic infection. Note the mildness of the cellular reaction. No Aschoff bodies or acute auricular lesions are present.

disease and its relation to the pathogenesis of the verrucous lesions will be discussed later in this paper.

**Microscopic Features.** Microscopically, the vegetations consisted essentially of agglutinated blood platelet thrombi (fig 6). In most instances there was already early evidence of organization, particularly

at the base and at the sides. The top of the thrombus was bare, but along the edges it was covered in part by an endothelial lining.

In eight cases the thrombotic material was superimposed on an irregular amorphous area of degeneration of the superficial portion of the valve substance, which we term eosinophilic change (fibrinoid) (figs 6, 7 and 8). This material gave a peculiar brownish green appearance with Van Gieson's stain and stained deeply with eosin. Often the vegetations were composed almost completely of this degenerative material, which seemed to be the result of the primary change and on which blood platelets were secondarily deposited from the blood stream.

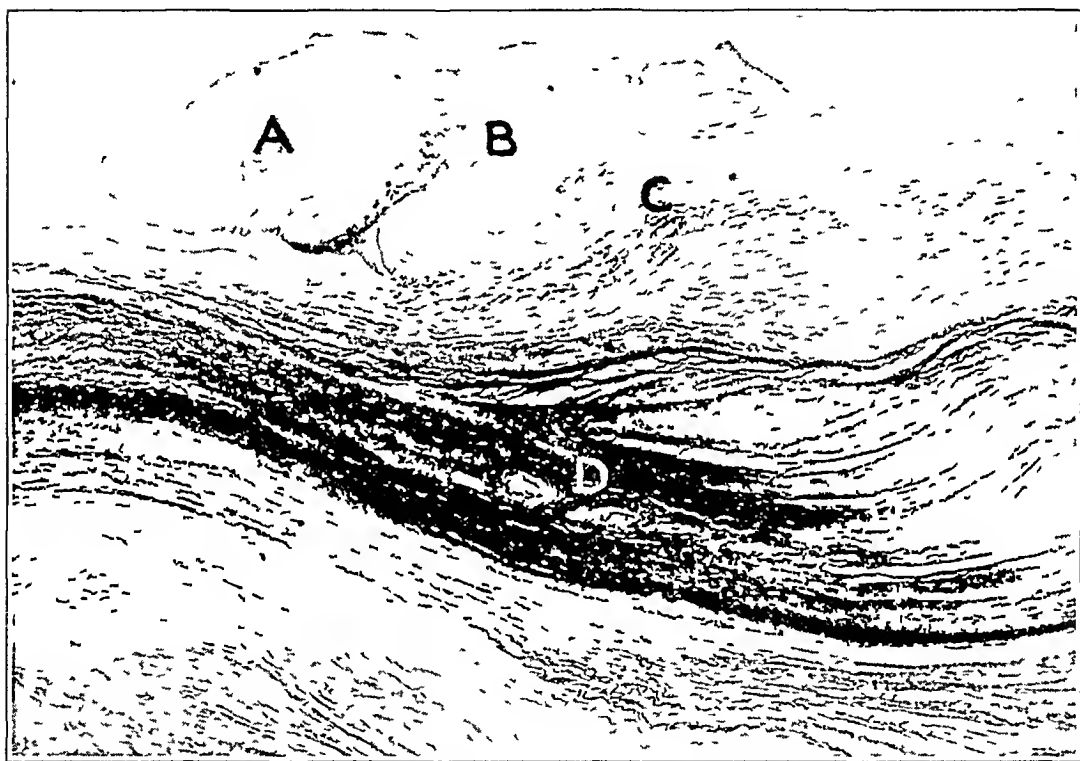


Fig 7—Nonbacterial thrombotic endocarditis of the mitral valve associated with rheumatic cardiovalvular disease. Low power photomicrograph of a section stained with Weigert's elastic tissue stain and Van Gieson's connective tissue stain. *A*, a recent blood platelet thrombus superimposed on and fused with *B*, eosinophilic change of an organized valve lesion. *C*, a mild cellular reaction. *D*, proliferation of the auricularis elastica, with considerable vascularization, probably evidences of a former rheumatic infection. No Aschoff bodies or acute auricular lesions are present.

The most remarkable feature of the histologic appearance of the valve was the absence or paucity of inflammatory reaction (figs 6 and 7). Usually, there was a slight cellular proliferation, with rare capillaries limited to the base of the vegetation where this was undergoing organization (fig 6 and 7). In no instance were there any polymorpho-

nuclear leukocytes, and rarely were there lymphocytes or plasma cells. Most of the proliferating cells appeared to be of the fibroblastic and histiocytic variety.

In about two thirds of the cases the vegetation was deposited on a markedly thickened fibrotic cusp, showing broad, sometimes partially hyalinized collagenous bands. In twenty-one cases these valves showed the subendothelial fibro-elastic reduplication and distortion commonly present in rheumatic fever (fig 8). In twenty cases the cusp was somewhat vascularized (figs 6 and 7). This was true particularly in the instances of definite old valvular deformities (probably rheumatic).

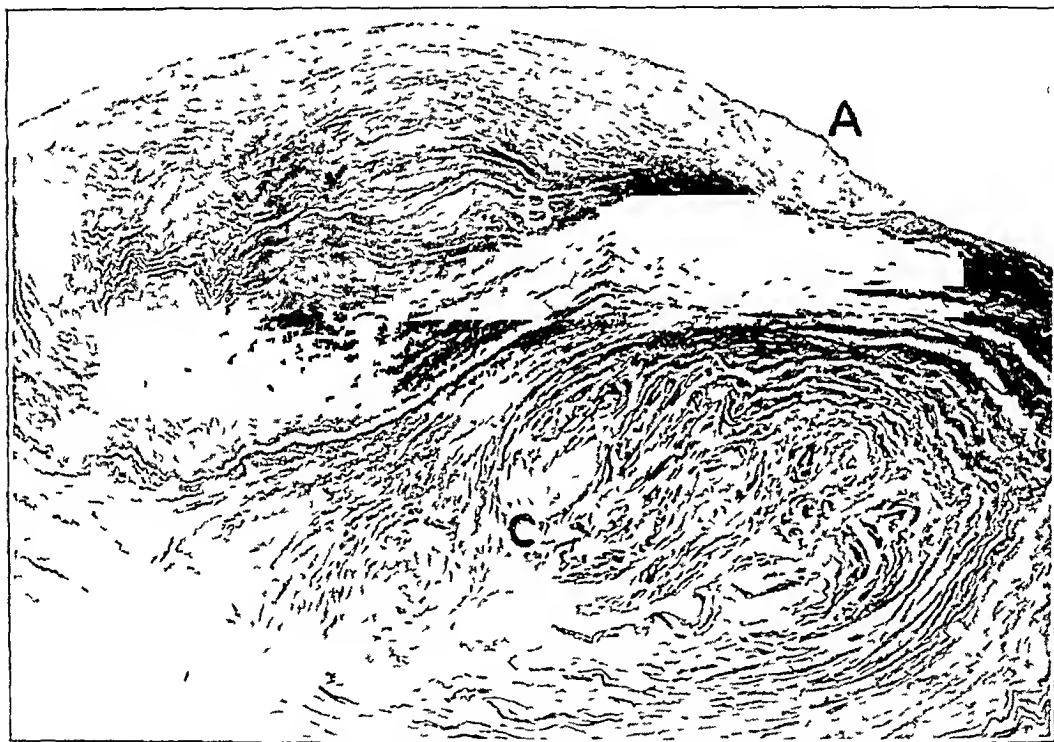


Fig 8—Nonbacterial thrombotic endocarditis of the mitral valve associated with carcinoma of the stomach. Low power photomicrograph of a section stained with Weigert's elastic tissue stain and Van Gieson's connective tissue stain. *A*, a remnant of vegetation deposited on the valve substance which has undergone eosinophilic change. Note the mildness of the cellular reaction. *B*, marked proliferation of the auricularis elastica, probably due to preceding rheumatic infection. *C*, chordae insertions. No Aschoff bodies or acute auricular lesions are present.

The slight degree of cellular proliferation and vascularization spoke for the inactivity of the rheumatic lesion.

*Lesions of the Valve Ring*—The limited area of fibro-elastic tissue which joins the cusp of a valve to the adjacent cardiac structures has been termed the valve ring (Gross and Kugel<sup>10</sup>). Its essential impor-

10 Gross, Louis, and Kugel, M. A. *Am J Path* 7:445-473, 1931.

tance lies in the fact that in rheumatic involvement of the valve the corresponding ring shows a fairly definite and characteristic inflammation. Among the cases of nonbacterial thrombotic endocarditis which we are discussing there was mild vascularization of the ring in thirty and slight infiltration with histiocytes, fibroblasts and occasional lymphocytes in fifteen. Involvement of the ring was confined almost entirely to the mitral valve. The lesions found were not those of active rheumatic fever but corresponded with changes in other parts of the heart indicating an old rheumatic infection.

*Auricular and Ventricular Endocardium*—In no case did we observe typical macroscopic or microscopic lesions of the endocardium of the left auricle, such as are associated with recent or active rheumatic endocarditis. However, in forty of the forty-seven cases we found the microscopic lesions which Gross<sup>11</sup> described in cases of rheumatic cardio-valvular disease in which there were no clinical evidences of recent rheumatic infection and no Aschoff bodies or other histologic evidences of active disease. These lesions consisted essentially of distortions of the auricular endocardial elastica, the presence of subendothelial proliferation, termed reduplications, and of mild lymphocytic infiltration and vascularization of the endocardium and subendocardium.

*Myocardial and Vascular Lesions*—The most striking vascular abnormalities occurred in the cases in which the condition was associated with thrombocytopenic purpura and with peculiar forms of involvement of the joints and of other serous membranes. Illustrations of these lesions appear elsewhere.<sup>12</sup> They consisted of proliferation, swelling and desquamation of the endothelium of the capillaries, arterioles and small arteries. Sometimes this proliferation led to localized verrucous or polypoid projections which encroached eccentrically on the lumen. More frequently the desquamated and degenerated cells formed granular plugs or hyaline thrombi, which partially or totally occluded the lumen. Occasionally endothelialized channels were visible in what had probably been organized granular or hyaline thrombi. Other vascular lesions corresponded to those described by Gross, Kugel and Epstein<sup>13</sup> as occurring in rheumatic fever, particularly in the peri-

11 Gross, Louis. *Am J Path* **11** 711-735, 1935.

12 (a) Friedberg, C K, and Gross, Louis. Nonbacterial Thrombotic Endocarditis Associated with Acute Thrombocytopenic Purpura, *Arch Int Med*, this issue, p 641. (b) Friedberg, C K, Gross, Louis, and Wallach, K. Nonbacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes, and Widespread Vascular Lesions, *Arch Int Med*, this issue, p 662.

13 Gross, Louis, Kugel, M A, and Epstein, E Z. *Am J Path* **11** 253-279, 1935.

adventitial region of the aorta and the pulmonary artery (Gross)<sup>14</sup> The interstitial myocardial lesions of active rheumatic fever were absent, but in six cases there were scattered foci of interstitial myocarditis consisting of polymorphonuclear leukocytes or lymphocytes, with areas of destruction and scarring, in the instances in which there were marked vascular lesions extensive focal areas of degeneration and replacement fibrosis were present

In summary, the condition in these cases was characterized pathologically by bland thrombi which were generally larger and often more friable than those characteristic of rheumatic fever Unlike those in atypical verrucous endocarditis, these thrombi were limited entirely to the valves The absence or paucity of recent inflammatory reaction in the cusps was characteristic In these respects nonbacterial thrombotic endocarditis is to be differentiated from other forms of endocarditis Finally, there was a marked tendency for this lesion to occur on scarred, thickened and deformed valves

#### SUBDIVISIONS OF NONBACTERIAL THROMBOTIC ENDOCARDITIS

When possible, classification of the conditions in these cases was based on the clinical syndromes with which the endocarditis was associated (table 2) In some cases these associated clinical syndromes were commonly known disease entities, such as glomerulonephritis and leukemia In seven cases, however, the associated clinical and pathologic manifestations presented unusual features requiring special study. Some of these are probably related to the conditions in the group of cases reported by Libman and Sacks,<sup>3</sup> Baehr, Klemperer and Schiffrin,<sup>15</sup> Tremaine<sup>16</sup> and Christian<sup>17</sup>

*Nonbacterial Thrombotic Endocarditis with Thrombocytopenic Purpura*<sup>12a</sup>—The three patients were young women Clinically, their symptoms were dominated by purpuric extravasations, epistaxes and other hemorrhagic manifestations The classic features of essential purpura haemorrhagica were present The septic course of the condition suggested a general infection, but cultures of the blood were sterile

At necropsy there was bland thrombotic endocarditis of the mitral valve in all three cases and of the aortic valve as well in one of them These valves showed verrucae of the conglomerate thrombotic type as well as the formation of ridges Microscopically, there were no

14 Gross Louis Am J Path **11** 631-645, 1935

15 Baehr, G, Klemperer, P, and Schiffrin, A Tr A Am Physicians **50** 139-155, 1935

16 Tremaine, M J New England J Med **211** 754-759, 1934

17 Christian, H A M Clin North America **18** 1023-1026, 1935

Aschoff bodies or other lesions of acute rheumatic infection. The presence of an old rheumatic lesion was likely in one instance and was probable in the other two.

There were marked vascular lesions in the heart and in other organs of one of the patients. These consisted of hyaline and granular plugs in various stages of organization. The condition was interpreted as a general disease, probably infectious, with hemorrhagic manifestations due to a toxic effect both on the endothelium of the capillaries and on the bone marrow.

*Nonbacterial Thrombotic Endocarditis with Arthritis, Inflammation of the Serous Membranes and Vascular Lesions*<sup>12b</sup>—This type, which was observed in four cases, also occurred in young women. There was a prolonged febrile course resembling a general infection, but numerous cultures of the blood were sterile. Polyarthritis, pericarditis, fibrinous pleurisy and pleurisy with effusion frequently dominated the picture. In two instances there was deforming arthritis, with fusiform joints. Ascites was recognized during life in one instance, and at necropsy there was subacute or subchronic polyserositis in all.

In addition to revealing the inflammation of serous membranes, necropsy showed rather characteristic grayish yellow friable vegetations of the conglomerate, or ridge, type on the mitral valve in each case, on the aortic valve in three and on the tricuspid and the pulmonic valve once each. There were vascular lesions resembling those described in the preceding group of cases. In one case there was, in addition, necrotizing panarteritis of the vessels of the myocardium, kidney, stomach and mesentery. The condition in this group was interpreted as a generalized infectious disease with marked affinity for endothelial structures.

*Nonbacterial Thrombotic Endocarditis with Cachectic and Infectious Disease Associated with Chronic Cardiovalvular Disease*—There were thirty-two patients with a variety of clinical diseases. However, all of them showed in common an old inflammatory lesion of the valves. This old lesion was probably rheumatic in the great majority of cases, but in one the thrombotic lesion occurred on an aortic valve which was deformed by calcification (Monckeberg<sup>18</sup> type). Although the verrucae themselves were recent, there were little or no valvular reaction, no Aschoff bodies and no acute pericarditis or acute auricular lesion. There was no history of rheumatic fever.

Five of the thirty-two patients presented diffuse glomerulonephritis. In three instances death occurred, with symptoms of failure of the right side of the heart apparently secondary to marked pulmonary emphysema and fibrosis with sclerosis of the pulmonary artery. In two other

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18 Monckeberg, J. G. Virchows Arch f. path. Anat. **176** 472-514, 1904.

patients with terminal symptoms of failure of the right side of the heart the primary cause seemed to be the valvular deformities themselves. In seven cases the essential clinical disease was carcinomatosis. There were apparently no symptoms directly referable to the endocardial lesions in these cases.

In general, we have found that when valvular verrucae are encountered in association with lobar pneumonia, they do not belong to the group of conditions which form the basis of this report. In the majority of instances such verrucae contain bacteria (that is, one is dealing with acute pneumococcic endocarditis) or the verrucae occur as part of an exacerbation of acute rheumatic endocarditis. However, in two instances there were fresh nonbacterial thrombotic vegetations occurring without simultaneous recent rheumatic disease and thus falling into the group under discussion. In each instance these occurred on definitely old rheumatic deformed valves.

There were ten additional patients with nonbacterial thrombotic vegetations superimposed on deformed rheumatic valves. The condition in these patients was associated with illnesses generally termed cachectic. In two cases the condition was uremia, due to malignant sclerosis and to arteriosclerotic contraction of the kidneys, respectively. There were two instances of acute leukemia and one of lymphadenosis, or pseudo-leukemia. There was one instance of acute miliary tuberculosis following posttonsillectomy pulmonary suppuration. One patient had chronic osteomyelitis and fibrinopurulent peritonitis, one died of a subarachnoid hemorrhage, one of purulent mediastinitis and one of cirrhosis of the liver.

The remaining three patients showed nonbacterial vegetations superimposed on deformity of the valve not due to rheumatic infection. In one these vegetations involved the mitral, aortic and tricuspid valves, which were the seat of marked sclerosis, in another they occurred on an aortic valve deformed by syphilis, and in the third, on an aortic valve which was the seat of calcific sclerosis of the Monckeberg type. All these three patients died of fibrinopurulent peritonitis.

*Nonbacterial Thrombotic Endocarditis Occurring on Relatively Normal Valves*—The occurrence of so-called terminal endocarditis in instances of cachectic disease is well known. Yet compared to the frequency of occurrence of the cachectic diseases, the percentage of cases of such endocarditis is extremely small. Certain of these thrombotic vegetations are of obvious bacterial origin, resulting from a terminal or terminating antemortem bacterial invasion of the blood stream. In the series of cases which we have studied, nonbacterial vegetations when present were in almost all instances superimposed on valves

already damaged by preceding, usually rheumatic, disease. There remains, nevertheless, a group of cases in which the valves appeared to be normal and in which the occurrence of previous rheumatic disease could not be definitely established. It must be borne in mind that the line dividing normal from abnormal valves is not a sharp one. We have employed as our conception of normal valvular structure that given by Gross and Kugel<sup>10</sup>. Furthermore, we have been guided by other anatomic criteria for the presence of recent and healed rheumatic disease, such as the evidences of healed auricular,<sup>11</sup> ring,<sup>10</sup> vascular<sup>13</sup> and root lesions<sup>14</sup>. These have been published in detail elsewhere. A more rigid point of view or more minute histologic examination of serial sections of the valves in the cases under discussion might have revealed that rarely or never did thrombotic vegetations in these cases occur on normal valves. On the other hand, a broader interpretation of normality might have included a few additional cases under this heading. In any event, the essential observation that in the great majority of our cases vegetations occurred on abnormal valves would still be pertinent.

In five instances nonbacterial thrombotic deposits occurred on presumably normal valves. Four of the patients died of carcinomatosis, one of uremia. These cases did not differ clinically in any significant respect from those of carcinomatosis or uremia in the preceding group.

*Unclassified Indeterminate Endocarditis*—There were three cases in which the condition could not be definitely allocated to any of the preceding types because the diagnosis clinically and after necropsy was obscure. One was an instance of severe anemia with hemorrhagic manifestations and high fever. The second was that of a woman of 42, who suffered from arthritis, pleural effusions, pneumonic symptoms, Raynaud's syndrome and fever. The third was that of a 21 year old girl, who had wild choreiform movements for three days, acquired hyperpyrexia (temperature 107 F) and died four days after hospitalization (fig 9). In all these cases there were nonbacterial vegetations on one or more of the valves.

*Nonbacterial Thrombotic Endocarditis Associated with Periarteritis Nodosa (Polyarteritis)*—Special mention should be made of the occurrence of periarteritis nodosa in two cases. Sacks<sup>20</sup> noted the association of periarteritis nodosa in several cases of indeterminate endocarditis. We have reported the association of periarteritis nodosa with active rheumatic heart disease<sup>21</sup>. One instance of nonbacterial

19 Gross, Louis, and Friedberg, Charles K. *Am J Path* **12** 469-493, 1936

20 Sacks, B. Personal communication to the authors

21 Friedberg, C. K., and Gross, Louis. *Periarteritis Nodosa (Necrotizing Arteritis) Associated with Rheumatic Heart Disease, with a Note on Abdominal Rheumatism*, *Arch Int Med* **54**:170-198 (Aug) 1934



thrombotic endocarditis associated with periarteritis nodosa fell into the subdivision associated with peculiar arthritis and involvement of the serous membranes. In the other case the condition was associated with glomerulonephritis and was placed in the subdivision of cases in which the condition was associated with cachectic and infectious diseases. It does not yet seem justifiable to group these cases in a separate subdivision, although further experience may indicate that this association of periarteritis nodosa and nonbacterial thrombotic endocarditis is no chance occurrence.



Fig. 9—Verrucous indeterminate endocarditis of the unclassified subdivision associated with a condition resembling acute chorea. Low power photomicrograph of a section stained with hematoxylin and eosin. *A*, an overhanging thrombus of the mitral valve. *B*, active granulation tissue reaction, contrasting with preceding illustrations of nonbacterial thrombotic endocarditis. *C*, flat thrombotic deposits nearer the base of the mitral valve superimposed on *D*, palisade formation.

#### COMMENT

Brief comments as to the etiology and pathogenesis of the endocarditis found in these cases appear pertinent. The direct etiologic agent is unknown, neither is it known whether the identical agent is responsible for the various types of nonbacterial thrombotic endocarditis. In our series a previous rheumatic involvement of the valves had

occurred in more than three fourths of the cases. Whatever the immediate precipitating cause, such preceding valvular damage appears to be the most significant predisposing factor.

Despite their frequent association with an old rheumatic infection, we are at present inclined to believe that the verrucae were of rheumatic origin, because of these considerations. While the verrucae were obviously fresh, the manifestations of rheumatic disease were those of an old, healed infection. There were no acute inflammatory changes in the auricular endocardium, pericardium, myocardium or valve cusps. Despite careful examination no Aschoff bodies could be found. There was no clinical evidence of a recent rheumatic infection which would



Fig 10—Unusually large rheumatic verrucae, grossly resembling those seen in nonbacterial thrombotic endocarditis. Microscopically typical rheumatic valvulitis with Aschoff bodies in the myocardium. *A*, grossly visible vascularization; *B*, verrucae on the anterior mitral cusp.

correspond with the age of the fresh verrucae. Nevertheless, the possibility that these verrucae are atypical manifestations of a rheumatic infection cannot be eliminated. The large size of the verrucae does not exclude a rheumatic etiology, as we have recently seen large polypoid rheumatic verrucae over 0.5 cm in diameter associated with typical rheumatic fever with Aschoff bodies in the myocardium (fig 10).

It should be noted that the condition in many of the cases included here must be classified also as belonging to type VI in the classification of the rheumatic valvular lesions (inactive lesions without Aschoff bodies) presented by Gross and Friedberg.<sup>6</sup> The term nonbacterial

thrombotic endocarditis is merely a descriptive classification of the secondary thrombotic deposits occurring on valves showing inactive rheumatic valvular lesions (type VI). Similar nonbacterial thrombi may be secondarily deposited on syphilitic valves or on valves showing the alterations of atypical verrucous endocarditis or of Monckeberg's sclerosis of the aortic valve or may occur as a primary change on apparently normal valves.

As far as we could determine, the verrucous endocarditis in these cases was not responsible for any clinical symptoms, nor was the course of the associated disease affected in any way. The association with many types of cachectic disease does not appear significant, because such endocarditis is decidedly infrequent in comparison with the tremendous number of necropsies on persons with such conditions as carcinoma, leukemia and uremia. We believe that the nonbacterial, nonrheumatic forms of verrucous endocarditis can occur as accidental insignificant complications of any fatal disease, especially when some previous disorder, usually rheumatic, has damaged the cardiac valves.

The conditions in the seven cases which constituted our first two groups showed certain clinical resemblances to atypical verrucous endocarditis which was described by Libman and Sacks<sup>3</sup> and to the cases of disseminated lupus erythematosus with extensive vascular lesions and a febrile clinical course which were reported on in detail by Baehr, Klempeier and Schiffrin<sup>15</sup>. None of our patients, however, showed the characteristic cutaneous manifestations described by these writers. Similarities are seen in the frequent occurrence in their cases of involvement of the serous membrane, of purpuric manifestations and of vascular and endocardial alterations. There is some question as to whether the presence of disseminated lupus erythematosus is an essential difference. It is conceivable that instances of the condition belonging to the general group described by Baehr and his co-workers might occur without the striking cutaneous lesions but with the other associated clinical and histologic features of the disease. It should be added, however, that aside from the absence of lupus erythematosus in our cases, the manifestations in the joints were more marked and produced more conspicuous deformities than those that occurred only occasionally in the cases of Baehr and his co-workers, the involvement of serous membranes was more extensive and dominated the clinical picture, and the vascular lesions were not entirely identical. Furthermore, the purpuric manifestations and the hematologic findings were never as marked in Baehr's cases as in those of our first group, in which they formed the essential clinical features.

Recently Tremaine<sup>16</sup> reported two cases of "subacute Pick's disease (polyserositis) with polyarthritis and glomerulonephritis," and later Christian<sup>17</sup> mentioned these two cases as instances of "long-continued

fever with inflammatory changes in the serous and synovial membranes and eventual glomerulonephritis, a clinical syndrome of unknown etiology." The condition in these cases presents many resemblances both to that in the cases of Baelr, as Tremaine pointed out, and to that in our cases in which there was involvement of the serous membrane (group 2). The condition in one of Christian's cases showed the features of disseminated lupus erythematosus. No special mention was made of vascular lesions, although an indirect reference to them was contained in Tremaine's description of the kidney. Despite the undoubted similarities of the conditions in these various groups of cases, definition of their exact interrelationship must be reserved until more is known of their etiology or until definite, rigid criteria can be set up for a clinical pathologic syndrome. For the present it is essential to call attention to this important group of conditions, so that they may be recognized when encountered clinically and so that they may be studied for further clarification.

#### SUMMARY

A study was made of one hundred and fifty cases with autopsy in which the condition was diagnosed anatomically as indeterminate, terminal or thrombotic endocarditis. In forty-seven cases there was microscopic evidence of fresh thrombotic vegetation, with little or no recent valvular reaction, without bacteria and without associated clinical or pathologic evidence of recent rheumatic infection or of atypical verrucous endocarditis. The condition was termed nonbacterial thrombotic endocarditis. The remaining one hundred and three of the original one hundred and fifty cases considered were discarded because careful histologic examination revealed bacterial endocarditis, recurrent rheumatic infection or hyalinized fibrotic tabs due to tension and degeneration or representing healed lesions of known forms of endocarditis.

A classification of endocarditis is presented. The position of nonbacterial thrombotic endocarditis in this classification is discussed. The forty-seven cases presented in this report fall into five subdivisions. Two of these, comprising three and four cases, respectively, appeared to possess clinical and pathologic features in common. In the first, the thrombotic endocarditis was associated with thrombocytopenic purpura and in one instance with widespread vascular lesions. In the second, the endocarditis was combined with widespread inflammatory involvement of serous membranes, with polyarthritis, sometimes of peculiar form, and with a variety of vascular lesions. The third group comprised thirty-two cases in which the endocarditis occurred in the course of a number of cachectic and infectious diseases, including carcinomatosis, leukemia, uremia, peritonitis and pneumonia. The distinguishing feature of this group was the occurrence of the vegetations

on valves which had invariably been deformed by preceding disease, usually by rheumatic inflammation. In a fourth, smaller, group, comprising four instances of carcinomatosis and one of uremia, vegetations were present on presumably normal valves. The fifth group comprised three cases in which the condition could not be classified.

Nonbacterial thrombotic endocarditis is viewed as an accidental occurrence in the course of any fatal disease, without appreciable clinical significance. Its development is probably dependent on previous damage to the cardiac valves. In our cases such previous damage was almost invariably due to an old rheumatic infection. While it does not seem probable that the verrucae in themselves were of direct rheumatic origin, this possibility must be borne in mind. In the first two groups of cases mentioned, the endocarditis might have been dependent also on some toxic agent which appeared to have a special predilection for endothelialized structures.

# NONBACTERIAL THROMBOTIC ENDOCARDITIS

ASSOCIATED WITH ACUTE THROMBOCYTOPENIC PURPURA

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In a previous description of nonbacterial thrombotic endocarditis we referred to two groups of cases which apparently had certain clinical and pathologic features in common<sup>1</sup>. The present report deals with one of these groups, which consisted of three cases of nonbacterial thrombotic endocarditis in which there was a clinical picture of thrombocytopenic purpura (fulminating in two cases), associated in one case with widespread vascular lesions. A later report will describe the second group of cases, characterized by prolonged fever, polyarthritides, inflammation of the serous membranes and vascular lesions<sup>2</sup>.

Purpuric manifestations are occasionally observed in other forms of endocarditis, particularly in bacterial endocarditis. In rheumatic fever purpura rarely occurs in a widespread, generalized form. In two of the four cases of atypical verrucous endocarditis described by Libman and Sacks<sup>3</sup> purpura was a significant symptom, and in one of them there was a reduction of the blood platelet count to 70,000 per cubic millimeter. In four of the eleven cases of the same disease described by one of us<sup>4</sup> the patients exhibited extensive purpuric symptoms, and two showed moderate thrombopenia. Recently, Baehr, Klemperer and Schiffrin,<sup>5</sup> in a study of twenty-three cases of disseminated lupus

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From the Medical Services and the Laboratories of the Mount Sinai Hospital.  
Aided by grants from the Lucius N. Littauer and the Walter W. Naumburg Fund.

1 Gross, Louis, and Friedberg, C. K. Nonbacterial Thrombotic Endocarditis: Classification and General Description, *Arch. Int. Med.*, this issue, p. 620.

2 Friedberg, C. K., Gross, Louis, and Wallach, K. Nonbacterial Thrombotic Endocarditis, Associated with Prolonged Fever, Arthritides, Inflammation of Serous Membranes and Widespread Vascular Lesions, *Arch. Int. Med.*, this issue, p. 662.

3 Libman, E., and Sacks, B. A Hitherto Undescribed Form of Valvular and Mural Endocarditis, *Arch. Int. Med.* **33** 701-737 (June) 1924.

4 Gross, Louis, in *Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues*, New York, International Press, 1932, vol. 2, pp. 527-550.

5 Baehr, G., Klemperer, P., and Schiffrin, A. *Tr. A. Am. Physicians* **50** 139-155, 1935.

erythematosis, noted the presence of widespread vascular lesions and endocarditis. There was a frequent tendency in these cases to thrombocytopenia and purpura.

In all these cases purpura was an incidental symptom largely overshadowed by other manifestations of the disease in question. The purpose of this report is to describe three cases of nonbacterial thrombotic endocarditis in which purpura and other hemorrhagic symptoms were the dominating clinical features of the disease. The blood studies were characteristic of purpura haemorrhagica. Certain features of the clinical course in two of the cases suggested that we had been dealing with a generalized, possibly infectious disease. The presence of widespread lesions of the vascular endothelium in one of the cases indicated the possibility that the hemorrhagic symptoms were the result not merely of a diminution of the blood platelet count but also of a toxic effect on the capillary endothelium. This case, together with three additional ones in which there were almost identical clinical and pathologic pictures, will be described in detail by Baehr, Klemperer and Schifrin<sup>6</sup>. In their report these authors link up the clinical data with the vascular lesions and discuss at length the pathogenesis of this syndrome.

#### REPORT OF CASES

**CASE 1<sup>7</sup>—History**—B. W., a 9½ year old girl, was admitted to the hospital in the service of Dr. Béla Schick, on Aug. 30, 1927. She had been suffering from headaches, listlessness, pallor, loss of weight and dyspnea for six months. In the six weeks preceding hospitalization she had had three attacks of hematuria associated with vomiting. Each attack lasted for several days and cleared up spontaneously. Her physician had made a diagnosis of nephritis. During the second attack, four weeks prior to her admission to the hospital there were "red spots" on the eyelids and later also on other parts of the body. She had had occasional bleeding from the gums. In the last week before her admission to the hospital pallor had become marked, and the skin had been tinged with yellow. In the last two days the temperature had been between 101 and 102 F.

**Examination**—The patient appeared chronically ill, mentally alert, well nourished, precociously developed, exceedingly pale and somewhat icteric. The temperature ranged from 101 to 104 F. The pulse rate was 140 and the respiratory rate 24 per minute. The blood pressure was 108 systolic and 58 diastolic. Over the flexor surfaces of the arms and over the trunk and extremities there were many bluish red purpuric spots ranging in size from that of a pinpoint to that of a pinhead. They did not blanch on pressure. The scleras were somewhat jaundiced and the conjunctivae pale. There was an ecchymotic spot on the conjunctiva of the left lower eyelid. In the fundus of the right eye just above the

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6 Baehr, G., Klemperer, P., and Schifrin, A. Tr. A. Am. Physicians, to be published.

7 This case is described and discussed in considerable detail by Baehr, Klemperer and Schifrin<sup>6</sup>. For a fuller description of the vascular lesions see their report.

disk there was a yellow area of exudate. There were ecchymotic spots on the buccal mucous membranes. The lungs were clear. The heart showed a slight, soft systolic murmur, heard best at the apex. The liver was felt 1 fingerbreadth below the costal margin. The spleen was just palpable. There was costovertebral tenderness on the right side.

*Provisional Diagnoses*—Various members of the staff offered the following diagnoses: a blood dyscrasia such as purpura haemorrhagica, hemolytic icterus or leukemia, subacute nephritis, and subacute bacterial endocarditis.

*Laboratory Examinations*—The blood count showed hemoglobin, 28 per cent, erythrocytes, 1,500,000, platelets, 25,000, leukocytes, 13,000, neutrophils, 81 per cent, eosinophils, 1 per cent, lymphocytes, 12 per cent, and monocytes, 6 per cent. The coagulation time was nine minutes, and the bleeding time, twenty-one minutes. The tourniquet test gave a positive result. There was no clot retraction in twenty-four hours. There were 20 per cent reticulated erythrocytes. The fragility of the erythrocytes was normal. The icteric index was 22. These studies were made by Dr. N. Rosenthal.

Roentgen examination of the nasal accessory sinuses revealed no abnormality. Roentgen examination of the abdomen showed no evidence of renal calculus, but the spleen appeared to be somewhat enlarged or situated low. Roentgen examination of the long bones showed no abnormality.

Electrocardiographic examination showed that the QRS complex was half inverted in lead III. The T wave was inverted in lead III, and the rate was 146 per minute.

The urine had a specific gravity of 1.020. It contained albumin (1 plus), a few granular casts and leukocytes and rare erythrocytes in centrifugated specimens. A twenty-four hour specimen of urine showed an increased amount of urobilin but no bile.

The direct van den Bergh test showed hemolysis. The indirect test showed a dilution of 1:25,000 (4 mg.).

Chemical analysis of the blood showed urea nitrogen, 23 mg. per one hundred cubic centimeters, nonprotein nitrogen, 50 mg., uric acid, 5.2 mg., and cholesterol, 124 mg. The Wassermann test of the blood was negative. Blood cultures on three occasions were sterile.

*Course*—Because of the marked anemia, the child was given two transfusions of citrated blood, each of 500 cc. of whole blood, with an interval of two days. The hemoglobin content rose from 28 per cent to only 34 per cent, and two days later it fell rapidly to 25 per cent. There was an increase in the quantity of urobilin excreted in the urine from 12.6 to 35 mg. in twenty-four hours. The platelet count varied between 20,000 and 40,000 per cubic millimeter of blood. The erythrocyte count was less than 1,500,000 per cubic millimeter of blood. The temperature continued to range between 100 and 102.6 F. The child's general condition grew progressively worse. Ten days after her admission to the hospital the hemoglobin content had fallen to 18 per cent. Splenectomy was performed after the patient was given 250 cc. of citrated blood. Another transfusion was given during the operation. She died suddenly at the conclusion of the operation.

*Postmortem Diagnosis*—The anatomic diagnosis was nonbacterial thrombotic endocarditis, hemorrhages in the skin, mucous membranes, pleura, peritoneum and renal pelvis, jaundice, anemia and multiple infarcts of the spleen and kidney.

*Gross Postmortem Examination*—The body was that of a well developed, well nourished girl. There was a greenish yellow, waxy pallor to the skin. The



scleras were jaundiced. There were numerous petechiae and purplish spots on the upper and lower extremities and on the trunk. The largest ones measured about 15 cm in diameter, the smallest were the size of a pinhead.

The heart was of normal size, weighing 210 Gm (fig 1). There were numerous small hemorrhagic foci beneath the pericardium. There was no pericarditis. The left auricle appeared normal. The anterior and most of the posterior mitral leaflet showed diffuse thickening with definite ridge formation on the line of closure. At about the middle of the anterior leaflet, and situated on the closure line, there was a large, oval thrombotic mass firmly attached to the valve by a broad base. The mass measured approximately 5 mm in width and 15 cm in length and was raised about 6 mm above the level of the cusp. Immediately anterior and somewhat inferior to this vegetation there was a smaller pendulous

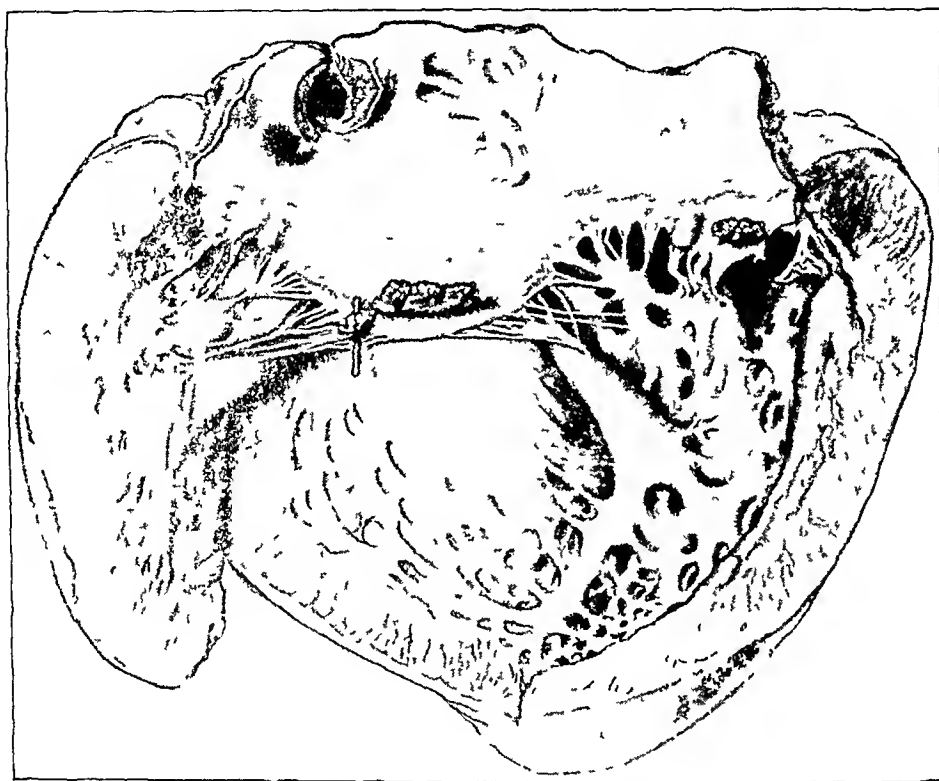


Fig 1—Nonbacterial thrombotic endocarditis (massive conglomerate type) of the mitral cusps

growth attached by a narrow pedicle. On the closure line of the posterior leaflet there was a similar but smaller thrombotic mass somewhat larger than a split pea. The thrombotic material consisted of confluent granular, friable vegetations. The chordae tendineae showed slight thickening. The left ventricular musculature was hypertrophied. The aortic valves were normal. The right auricular chamber was somewhat dilated. A slight granular thickening was noted on the right cusp and a subendocardial hemorrhage above the insertion of the anterior cusp of the tricuspid valve. The right ventricle was slightly hypertrophied. The pulmonic cusp was normal.

The lungs showed subpleural hemorrhages. There was some cloudy swelling of the liver. Both kidneys showed several large, old infarcts.

The spleen, which was removed at operation, was about one and one-half times the normal size and contained two small yellowish infarcts extending to the periphery in cone shapes. An accessory spleen was present in the gastrosplenic omentum.

*Microscopic Postmortem Examination*—Examination of the heart showed that there was no endocardial lesion in the left auricle. The ring of the posterior mitral valve contained a few round cells and capillaries. The cusp itself was slender. About midway along the cusp there were mushroom-shaped projections on the auricular surface external to the subendothelial elastica, consisting of proliferated cells, mostly histiocytes, fibroblasts and lymphocytes. In the center there was scarring. On either side endothelial proliferation was present. There was no

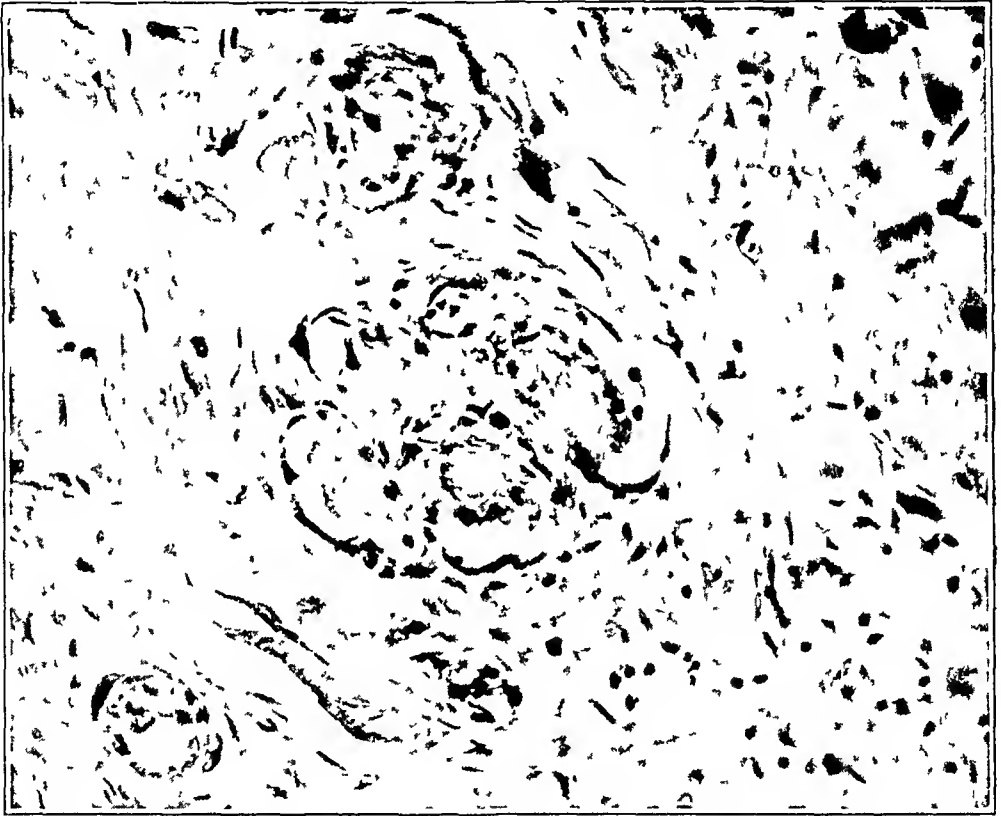


Fig 2—Myocardium of the left ventricle. Hematoxylin and eosin stain, high power. Note the vessel in the center with granular plugs and recanalization of the lumen.

reaction in the cusp. The anterior cusp of the mitral valve appeared normal except for the region of the closure line, where the auricular portion of the valve was thickened and the elastica was proliferated. The endothelial layer was necrotic and replaced by fibrinoid material. Superficial to this and apparently broken off from it was a large, pendulous thrombotic mass containing fibrin, blood platelets and a few leukocytes. At the sides of the base there was early organization. In the cusp itself practically no reactive inflammation was present. Slight scarring and a few capillaries were noted in the ring of the tricuspid valve. Otherwise the tricuspid and pulmonary valves were normal. The myocardium showed diffuse, small, irregular areas of destruction and replacement fibrosis. The vessels showed widespread abnormalities throughout. Many of the capillaries and smaller

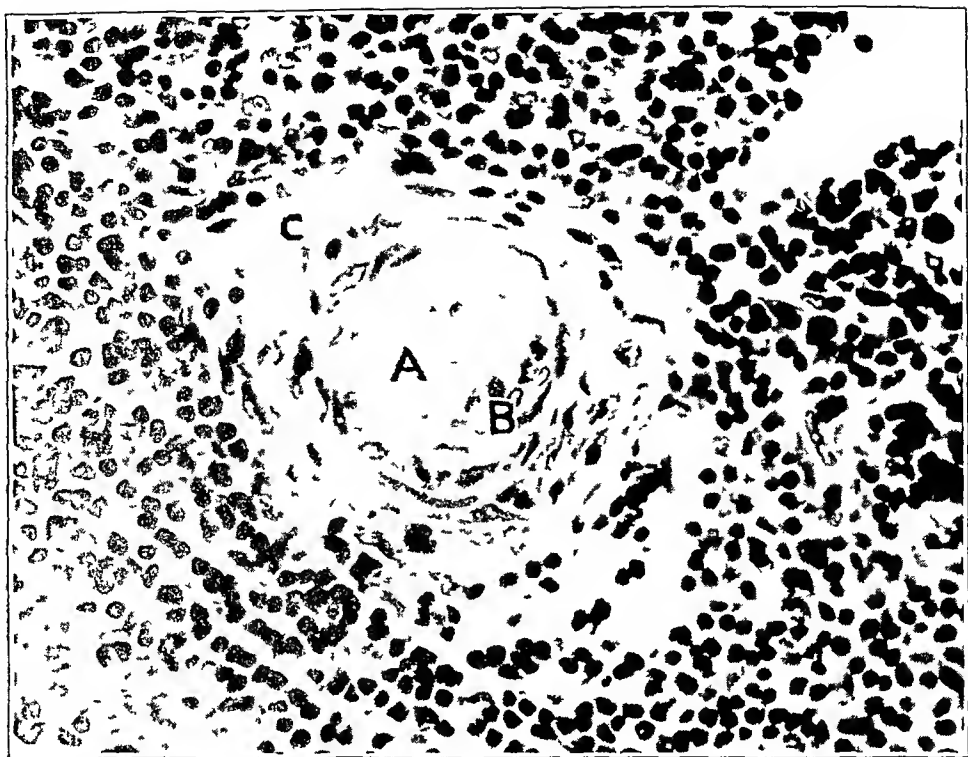


Fig 3—Splenic arteriole Hematoxylin and eosin stain, high power *A* indicates a granular thrombus plugging the lumen, *B*, endothelial proliferation (note the disorientation of the vessel layers), and *C*, adventitial edema



Fig 4—Renal arterioles with occluding granular plugs Hematoxylin and eosin stain, low power

arteries were partially or completely plugged by hyaline or granular degenerating masses. The endothelium was proliferated or desquamated, sometimes forming eccentric polypoid masses projecting into the lumen. Some of the capillary and arteriolar plugs showed recanalization (fig 2).

In the lung there were edema and exfoliation of cells into the alveoli. Sections of the liver showed fatty and granular degeneration of the cells. The pre-capillary branches of the hepatic artery contained granular plugs, some of which were canalized. In the spleen there were multiple areas of necrosis about the malpighian corpuscles, and surrounding the areas of necrosis were zones of hemorrhagic reaction. The blood vessels were hyalinized and contained granular masses (fig 3). The vessels of the kidney showed similar alterations. There were hyaline plugs in several of the larger arteries (fig 4). Some of the glomeruli showed hyaline plugs in the tufts, varying from a small focus to the entire glomerulus. Some of the tubules contained hyaline casts. The capsule of the adrenal gland was thickened and congested. Many of the vessels in the cortex contained hyaline plugs.

*Comment*—The symptoms in this case were essentially those of hemorrhagic disease. Because of the prolonged bleeding time (twenty-one minutes), the marked reduction in the number of platelets (25,000 per cubic millimeter), the presence of the Rumpel-Leede phenomenon and the absence of clot retraction, a diagnosis of purpura haemorrhagica seemed most likely. The septic course associated with continued fever, cardiac murmur, splenomegaly, hematuria and petechiae suggested the possibility of subacute bacterial endocarditis. Blood cultures were sterile on three different occasions.

Despite repeated transfusions and splenectomy, the patient did not recover. At necropsy there was widespread evidence of vascular disease characterized by the presence of hyaline and granular plugs in the capillaries and small arteries of the heart, liver, spleen, kidneys and adrenal glands and in some of the veins of the heart. In some instances the plugs were endothelialized, and new channels had formed in the lumens. The endothelium was desquamated or proliferated to form polypoid or verrucous masses which projected into the lumen and diminished its size. Baehr, Klemperer and Schiffrin stated that they believed that the plugs were primarily platelet thrombi, which in later phases become organized by endothelial proliferation. Large friable verrucous lesions were situated on both cusps of the mitral valve. The vegetations were composed of a blood platelet thrombus which was undergoing early organization. Bacteria were absent. There was practically no reaction in the cusps. There were no Aschoff bodies or other evidences of acute rheumatism.

*CASE 2—History*—E. K., a 21 year old milliner, was first admitted to the hospital, in the service of Dr. G. Baehr, on March 17, 1928. She had been treated in the outpatient department of the Mount Sinai Hospital for bleeding gums for one year and for nosebleeds for six weeks. Her past history included a nervous breakdown two years previously and simple enlargement of the thyroid gland.

since puberty. She had had occasional nosebleeds (about three or four times each year) for the past ten years, the nosebleeds lasting generally for about one-half hour. In the preceding six weeks, however, these episodes had become more frequent and more severe, there having been eight nosebleeds in that interval which occurred spontaneously and lasted for about an hour. The gums had bled daily for the past year, but her dentist could find no local condition in the mouth to account for this. The patient said that black and blue spots had always developed after even slight injury. In addition, she had had clubbed fingers as long as she could remember.

*Examination*—The patient appeared well developed, well nourished and not obviously ill. The size of the heart was normal, but there was a rough, prolonged, low-pitched systolic murmur following the first sound, heard best at the apex. The thyroid gland was symmetrically and moderately enlarged, and systolic and diastolic bruits were heard over it. There was incurvation of the finger-nails and a suggestion of clubbing. There were many purpuric and ecchymotic areas over both upper and lower extremities. The spleen was not palpable. The blood count showed hemoglobin, 72 per cent (100 per cent equals 17 Gm), erythrocytes, 5,100,000, leukocytes, 6,000, platelets, 168,000, neutrophils, 67 per cent, lymphocytes, 25 per cent, and mononuclears, 8 per cent. The tourniquet test showed a positive result. The bleeding time was two minutes, and the coagulation time, eleven minutes. There was slight clot retraction after two hours.

In the outpatient department three weeks earlier, the hemoglobin value had been 90 per cent, the platelet count, 80,000, the bleeding time, nine minutes, and the coagulation time, eighteen minutes. The urine showed a specific gravity of 1.022, albumin (1 plus) and occasional leukocytes.

*Provisional Diagnosis*—A diagnosis of purpura haemorrhagica was made, but because of the association of slight fever, clubbing of the fingers and a cardiac murmur, a blood culture was made to verify the possible diagnosis of bacterial endocarditis. The culture was sterile. The Wassermann test was 4 plus on two occasions, and antisiphilic therapy was started. There were no nosebleeds during the patient's stay in the hospital, and she was discharged with the diagnosis of chronic thrombocytopenic purpura.

*History*—The patient was readmitted on April 24, 1933. In the interval she had had one or two nosebleeds monthly, usually just before or after the menses. She had suffered also from bleeding of the gums and had occasionally noted blood in the stools. The last menstrual period had lasted for two weeks. The immediate cause of hospitalization was severe epistaxis which had not been controlled after five hours.

*Examination*—On this occasion the patient was pale, and both nostrils were filled with blood-soaked, oozing cotton. There was a small linear hemorrhage below the disk in the right fundus. There were multiple ecchymotic areas over the lower extremities and a few on the abdomen. The heart was enlarged to the right and left, and there was a blowing systolic murmur over the apex and to the left of the sternum. The blood pressure was 136 systolic and 80 diastolic. The liver was palpable 1 fingerbreadth below the costal margin and was slightly tender. The spleen was not palpable. The diagnosis was thrombocytopenic purpura.

The blood count showed hemoglobin, 52 per cent, erythrocytes, 3,000,000, leukocytes, 7,400, neutrophils, 84 per cent, lymphocytes, 10 per cent, monocytes, 6 per cent, color index, 0.9, and platelets, 90,000. The coagulation time was four

minutes, and the bleeding time, forty-one minutes. Clot retraction was poor. The tourniquet test gave a positive result.

The urine contained a trace of albumin, many leukocytes and occasional erythrocytes. The Wassermann test of the blood was 4 plus; the Kahn test, negative. The urea nitrogen content of the blood was 13 mg per hundred cubic centimeters. The blood pressure was 100 systolic and 74 diastolic. The pulse rate was between 100 and 110 per minute, and the temperature was between 100 and 103 F.

The nasal cavity was packed, snake venom was injected and transfusions and antisyphilitic drugs were given, without satisfactory control of the bleeding. On May 10, 1933, the splenic artery was doubly ligated, with the patient under spinal anesthesia, and a transfusion of 500 cc of whole blood was given. Repeated examinations of the blood revealed that the platelet count was around 50,000 per cubic millimeter and that the hemoglobin content was about 50 per cent. There was an intermittent tendency to mild bleeding from the gums.

*History*—The patient's third admission to the hospital was on Oct 18, 1933. Death occurred within twenty-four hours. In the interval since her last discharge from the hospital she had felt well despite slight bleeding from the gums. The menstrual bleeding had been normal, and she had gained in weight and strength. There had been one nosebleed four weeks before her third admission to the hospital. This was easily controlled. Three weeks before her admission to the hospital she began to bruise with unusual ease, the nose and gums bled more frequently and profusely and she felt weak, dizzy and faint. Five days preceding hospitalization she began to menstruate, but the bleeding was abnormally profuse and persistent. She complained of headache, dizziness, weakness, nausea and sharp abdominal pain.

*Examination*—The patient was acutely ill, febrile and pale. The pulse rate was 120 per minute. The blood pressure was 132 systolic and 76 diastolic. There were spongy, oozing gums, petechiae over the face, legs and flanks and large ecchymotic blotches over the thighs and forearms. The remainder of the observations were the same as those made previously. The hemoglobin content was 34 per cent, and there were 1,980,000 erythrocytes and 30,000 platelets per cubic millimeter of blood. The spinal fluid was normal. A transfusion of 500 cc of whole blood (Unger method) was given, after which the temperature mounted rapidly to 105 F. The patient became comatose, and the extremities grew flaccid. She died from an intracranial hemorrhage the next day.

*Postmortem Diagnosis*—The anatomic diagnosis was secondary anemia, non-bacterial thrombotic endocarditis of the mitral valve, hemorrhagic ascites, bilateral pleural hemorrhagic effusions, generalized ecchymoses of the skin and several mucosal surfaces, bilateral hemorrhagic cysts of the ovaries, subdural hematoma (right), pulmonary edema, perisplenic adhesions, acute infectious splenic tumor, vascular atrophy of the kidneys, parenchymatous degeneration of the viscera and persistent thymus.

*Gross Postmortem Examination*—The body was that of a well developed, well nourished woman. There were purplish red petechiae and ecchymoses in the skin ranging from the size of a pinhead to that of a 5 cent piece, many of which were fading. On the inner aspect of the left thigh there was a large ecchymotic area with a purplish red border and fading center. There were a few hemorrhagic petechiae over both lower extremities and forearms.

The heart was somewhat enlarged and globular. The pericardium was normal except for a few circumscribed adhesions on the posterior aspect of the right auricle. There were several epicardial petechiae. The left auricle appeared normal.

The mitral valve was for the most part thin and translucent, but along most of the closure line of both cusps there were interrupted pyramidal ridges which were firm, brown and elevated about 7 mm above the surface of the valve. One large ridge was situated along the middle of the anterior cusp, and two somewhat smaller ones, but of similar appearance, on the posterior cusp. These ridges appeared to be made up of, or capped by, fused flat irregular white nodules. There was no gross vascularization. The chordae tendineae were normal. The left ventricular cavity was slightly dilated, and its musculature was somewhat hypertrophied. The anterior papillary muscle was streaked with fat. The aortic valves were normal. The right auricular endocardium appeared normal. The tricuspid valves, the right ventricle and the pulmonary valves likewise showed no abnormality.

The lungs weighed 1,600 Gm. They were slightly edematous and contained petechiae and purpuric areas on the pleural surfaces. There were somewhat raised, circumscribed, oval reddish granular areas in the lower lobes. The liver weighed 1,650 Gm and contained subcapsular hemorrhages. The spleen was markedly enlarged, weighing 300 Gm. It was soft and reddish brown, and its pulp scraped with ease. The follicles could not be distinguished. The splenic artery was obliterated. The kidneys were much smaller than normal, both together weighing 170 Gm. They were pale, yellow-red and flabby, with many subcapsular hemorrhages. There was some difficulty in stripping the capsule. The surface was irregular, finely granular and covered with hemorrhages. The cortex was narrow and irregular. The gastro-intestinal tract was normal except for subserosal and submucosal hemorrhages. There was a subdural hematoma in the right side of the brain.

*Microscopic Postmortem Examination*—Examination of the heart showed that there was no acute lesion of the left auricular endocardium. There was a focal area of organizing lymphocytic pericarditis. The ring of the posterior mitral valve appeared normal. On the auricular surface of the cusp near the closure line there was a large hyalinized knob composed of broad masses of collagen fibers with few cells. The surface was capped by a thrombus of blood platelets. At the sides the nodule was covered with endothelium. Its base was organized and contained two small foci of lime. There was no cellular reaction or vascularization of the cusp, but the cusp was moderately thickened. At the tip there was increased proliferation of histiocytes. On the auricular surface and at the closure line of the anterior mitral cusp there was a large nodule similar to that on the posterior cusp. It was hyalinized and acellular. At the edges, however, there was slight cellular reaction. There was moderate histiocytic proliferation of the tip. The remainder of the cusp was normal. The aortic valve was normal. There were a few capillaries and round cells in the ring of the pulmonic cusp, otherwise it was normal. The tricuspid valve likewise was normal except for a few capillaries in the ring. In the myocardium there was occasional endothelial proliferation of the smaller vessels. There were irregular diffuse areas of scarring in the ventricular myocardium.

In the lungs there were large areas of hemorrhage, with edema and desquamated epithelial cells in the alveoli. There was severe autolysis of the renal parenchyma. The subcapsular glomeruli were hyalinized or fibrosed, the less superficial ones were well preserved. The small and medium-sized blood vessels were markedly narrowed and often entirely closed by endothelial proliferation, while the larger vessels were partially occluded by hyaline intimal thickening and elastic reduplication. The renal arteries of moderate size showed marked elastic reduplication.

The splenic pulp was crowded with red blood cells. There were also many polymorphonuclear leukocytes. A few megakaryocytes were seen. The smaller blood vessels showed marked intimal fibrosis and slight endothelial proliferation. The bone marrow from a vertebra showed activity, with many myeloid cells of all types. The liver showed moderate degeneration.

*Comment*—This patient had been subject to bleeding from the gums, black and blue spots and severe nosebleeds for a long time and on three occasions had required hospitalization. The hemoglobin content originally was 90 per cent, but it had progressively diminished to 34 per cent, and the red cell count had decreased to 1,980,000 per cubic millimeter of blood. There were 80,000 platelets per cubic millimeter. The bleeding time was markedly prolonged, and there was poor clot retraction. The Rumpel-Leede phenomenon was present. While the diagnosis of purpura haemorrhagica appeared obvious, the association of fever, clubbed fingers and a rough prolonged systolic murmur at the apex of the heart again suggested subacute bacterial endocarditis. In this case the purpura was considered to be a toxic manifestation of that disease. This suggestion was not confirmed by repeated blood cultures, which were sterile. Various forms of therapy, including packing the nasal cavity, injecting snake venom and the repeated giving of transfusions, were ineffective. Ligation of the splenic artery gave a temporary remission, but the patient finally died apparently of intracranial hemorrhage.

At necropsy in addition to numerous hemorrhages there was a partially organized blood platelet thrombus on the mitral valve, with little inflammatory reaction in the cusp itself. The vascular lesions were slight in comparison with those in the previous case and were of dubious significance. The only marked lesions were in the kidneys, but these were interpreted as being secondary to pyelonephritis, although no renal symptoms were mentioned in the clinical history. The spleen was somewhat larger than it ordinarily is in a patient with idiopathic purpura haemorrhagica and showed acute hyperplastic and inflammatory changes (acute splenic tumor).

*CASE 3—History*—M. S., a 30 year old saleswoman, was admitted to the hospital, in the service of Dr. E. Libman, on Jan. 14, 1923, complaining of a feeling of dulness for two days and anuria for one day. Five years previously she had had a "nervous breakdown." At that time she suffered from blueness and coldness of the hands and vague pains in the hands, fingers, back and knees. She was told that she had rheumatism. Shortly afterward she was confined to bed for about eight weeks with an attack of pleurisy. The vague pains in the extremities had persisted up to the day of her admission to the hospital. The tonsils were removed three months previously because of these pains. Following this operation the pains in the extremities became worse, and precordial pain was present for about ten days. For the past six months the gums had bled somewhat severely, even more markedly after tonsillectomy. Two weeks before her admission to the hospital she had a temperature of 102° F. for an entire week. Three days before she



entered the hospital her physician discovered a small hemorrhage in the conjunctiva of one eye. The next day she began to feel dull, drowsy, feverish and irritable. Her appetite had become poor, and coughing and expectoration were noted. For the past twenty-four hours she had been unable to urinate.

*Examination*—The patient was an obese, acutely ill, toxic, pallid, mentally dull, dyspneic woman who coughed at intervals and raised small amounts of mucopurulent, slightly blood-tinged sputum. The temperature was 104.4 F, the pulse rate 138 and the respiratory rate 32 per minute. The blood pressure was 115 systolic and 60 diastolic. There was slight exophthalmos. The scleras were subicteric and the conjunctivae pale. There was a hemorrhage in the right fundus, the retinal veins were engorged and the arteries were tortuous. There was a small whitish area of exudate in the fundus of the left eye, and the disk margins were blurred on the right. The gums were bleeding. There were irregular ecchymotic areas and a small ulcer on the right side of the buccal mucosa, purpuric extravasations and small glistening lesions on an erythematous base on the hard palate. The sternum was tender. The lungs were dull to percussion over the lower three fourths of both sides posteriorly and over the lower half of both axillary regions. The breath sounds were diminished over these areas. There was feeble bronchial breathing, and bronchophony was noted at the angle of the left scapula. Subcrepitant rales were audible over the areas which were dull on percussion. The apex beat of the heart was seen and felt in the fifth interspace outside the nipple line. Percussion showed that the heart was enlarged to the left, extending 14.5 cm in the fifth and 7 cm in the second space from the midsternal line. There was a short, soft systolic murmur over the pulmonic area. The second pulmonic sound was accentuated and louder than the second aortic sound. The abdomen was slightly distended. The right kidney was palpable and somewhat tender. Over the dorsum of the left foot there were long, irregular, nonindurated, nontender purpuric extravasations. On the outer aspect of the right leg and on the pad of each thumb there were irregular nontender purpuric spots.

*Provisional Diagnoses*—The diagnoses made included bilateral bronchopneumonia, toxic purpura, chronic nephritis (?) and sepsis (?)

*Laboratory Examination*—The blood count showed hemoglobin, 59 per cent (Kuttner, corrected), erythrocytes, 3,312,000, leukocytes, 13,800, platelets, 8,000, neutrophils, 94.6 per cent, lymphocytes, 3.3 per cent, monocytes, 0.6 per cent, and myelocytes, 1.3 per cent. The bleeding time was six minutes and the coagulation time eleven minutes. The tourniquet test showed a positive result. There was no clot retraction.

The Wassermann test of the blood was negative. Chemical analysis of the blood showed urea nitrogen, 15.4 mg per hundred cubic centimeters, incoagulable nitrogen, 37.6 mg, uric acid, 5.4 mg, and creatinine, 1.4 mg. A blood culture was sterile. The urine had a specific gravity up to 1.025 and contained albumin (3 plus), occasional casts, many single leukocytes and a few erythrocytes. The phenolsulfonphthalein test showed 25 per cent recovered in two hours.

*Course*—The patient's temperature ranged between 103 and 105 F. The pulse rate was between 120 and 160 and the respiratory rate between 30 and 60 per minute. She became progressively drowsier and then incontinent. The skin and scleras became icteric. There were fresh erythematous areas over both feet and purpura over the buccal mucosa on the left and over the sternum. On January 17 there was frank consolidation at the base of the left lung, and a pleural friction rub was heard over the precordium. The next day pulmonary edema was present. The patient vomited bloody fluid and died.

*Postmortem Diagnosis*—The anatomic diagnosis was nonbacterial thrombotic endocarditis (mitral and aortic valves), acute fibrinous pericarditis acute lobar pneumonia, jaundice and splenomegaly

*Gross Postmortem Examination*—The body was that of an obese, well developed woman. The scleras and skin were light yellow. Over the skin of the trunk and extremities there were a large number of purpuric spots varying in size and shape, the average diameter being 2 or 3 cm.

The heart was enlarged, weighing 600 Gm. There was shaggy pericarditis, especially on the posterior surface. The mitral valve was thickened. Along the line of closure of both cusps there was a golden yellowish, gelatinous, interrupted



Fig 5—Nonbacterial thrombotic endocarditis of the posterior mitral cusp. Weigert's elastic tissue stain and Van Gieson's connective tissue stain, low power. A, a huge vegetation occupies the region above the arrow. A indicates a blood platelet thrombus, B, an organized base of vegetation (note that the remainder of the vegetation is composed largely of swollen eosinophilic material), C, an auricularis layer (note the absence of inflammatory reaction), D, a marked increase of the auricularis elastica, and E, a muscular blood vessel (evidence of an old rheumatic process).

ridge of verrucae with an overhanging border and firm base, each portion of the ridge being about 1 cm in length. On this ridge were a few translucent glistening granules the size of a pinhead. The chordae tendineae and their junctions with the valve were normal. The aortic valve showed on its posterior cusp a mound of heaped-up verrucae near the corpus Arantii. This consisted of numerous confluent, friable, grayish yellow deposits the size of a pinhead. In addition there was

a toothlike line of tiny verrucae on the right aortic cusp. The free edges of the valves were thin. The other valves were essentially normal. The lungs weighed 1,200 Gm. There were large areas of consolidation in the lower lobes of both lungs and in the upper lobe of the left lung. The abdomen contained a small amount of ascitic fluid. The liver weighed 1,800 Gm. Chronic passive congestion, cloudy swelling and diffuse jaundice were noted. The spleen was markedly enlarged, weighing 400 Gm. The malpighian bodies were enlarged, and the pulp was intensely congested, with an apparent cellular increase. The kidneys weighed 400 Gm together. The capsules stripped with some difficulty, revealing a fairly granular surface. A cut section showed marked congestion and cloudy swelling.

*Microscopic Examination*—The pericardium showed organizing pericarditis. There was a moderate amount of interfascicular fibrosis in the myocardium. No

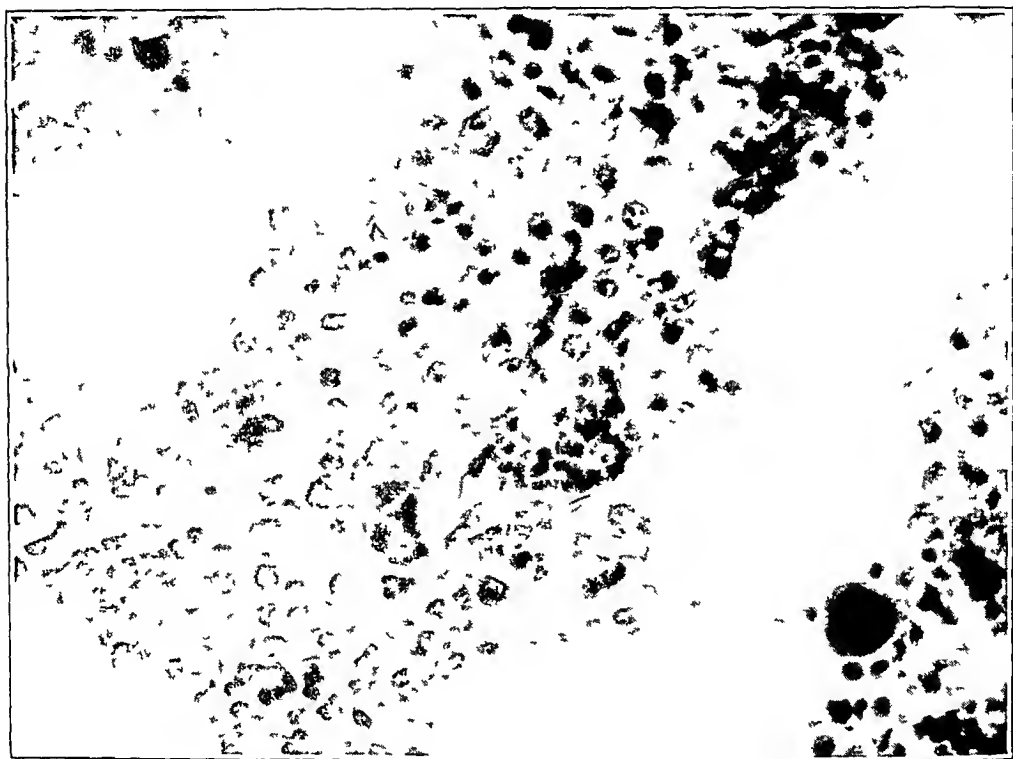


Fig 6—Bone marrow. Hematoxylin and eosin stain, high power. Note the normal cellular constituents, including megakaryocytes.

Aschoff bodies could be seen. There was no acute lesion of the auricular endocardium. The mitral valve was somewhat thickened. Fibrosis and vascularization of the ring were noted. At the base of the cusp there were several small arterioles with thick muscular coats. The cusp itself was moderately thickened, especially in the region of the closure line. This thickening affected chiefly the auricularis layer, which consisted of the broad bands of hyalinized connective tissue. The most superficial portion was capped by broad amorphous plaques of degenerated material, staining deeply with eosin and brownish green with Van Gieson's stain (fig 5). Only a few ghosts of cells remained in this material, which we call eosinophilic swelling (fibrinoid change). There was seen slight cellular reaction, consisting only of a few lymphocytes at the base. At either side of the

vegetation there were thick-walled vessels within the substance of the cusp. In one section this eosinophilic material was covered by a broad, massive thrombotic deposit consisting of fibrin and blood platelets partly hyalinized and partly organized. The elastica of the mitral cusp was reduplicated and distorted beneath the region of the vegetation. The section of the posterior aortic cusp through the vegetation in the region of the corpus Arantii showed a thin cusp except at the level of the closure line. At that point the subendothelial fibro-elastic layer was markedly thickened and reduplicated. Superficially, there was a huge thrombotic deposit undergoing organization at the base, partly hyalinized and superficially capped by blood platelets. There was practically no cellular reaction, and only a few blood vessels were present at the base of the thrombus. Nearer the attachment of the cusp the subendothelial layer contained a row of somewhat thickened blood vessels. The right auricle showed a small area of inflammation containing blood vessels and lymphocytes. The tricuspid and pulmonic valves were essentially normal. In the region behind the pulmonary artery the vessels showed marked proliferation of the elastica and medial hypertrophy.

In the lungs were areas of lobar pneumonia and bronchopneumonia, as well as purulent bronchitis and extensive hemorrhages in the alveoli. There was focal nephrosclerosis. The liver showed moderate fatty infiltration. The sinuses of the spleen were dilated and congested. The bone marrow showed many megakaryocytes (fig 6).

*Comment*—This patient entered the hospital because of severe acute infection of the upper respiratory tract. Examination showed that there were widespread ecchymotic areas in the skin and mucous membrane of the mouth, icterus, high fever, signs of pneumonia, cardiac enlargement, an apical systolic murmur and accentuation of the second pulmonic sound. A diagnosis of bilateral bronchopneumonia was made. The purpura was considered to be a toxic manifestation of the disease. However, because the hemorrhagic symptoms were of six months' duration and because the blood showed the characteristics of purpura haemorrhagica, including a platelet count of 8,000 per cubic millimeter, that interpretation was discarded.

At necropsy organizing pericarditis and nonbacterial thrombotic endocarditis involving the mitral and aortic valves were present. There was no evidence that the recent verrucae were of rheumatic origin. There was, however, evidence of healed rheumatic infection in the mitral and aortic valves. In view of the evidence of previous rheumatic disease and the presence of organizing pericarditis, the occasional lesions in the heart were not considered to be of any special significance. The spleen was considerably enlarged, congested and soft.

#### COMMENT

After the observations on the reduction of the blood platelet count in certain forms of purpura by Hayem,<sup>8</sup> Denys<sup>9</sup> and others, these elements became the central point in the classification of purpuric disease

8 Hayem, E. *Presse med* 3 233-235, 1895

9 Denys, J. *Cellule* 3 445-461, 1887

Two large groups were set up, the thrombocytopenic and the athrombocytopenic purpuras, depending on the presence of either a markedly diminished or a normal number of blood platelets. The former group includes idiopathic or essential purpura haemorrhagica or morbus maculosus Werlhofii, the blood in these cases showing, in addition to thrombopenia, an increased bleeding time, the Rumpel-Leede phenomenon and absence of clot retraction. The other group included the Henoch-Schonlein purpura, in which the blood picture is essentially normal. Further studies have indicated that such a dualistic grouping on the basis of the number of blood platelets is artificial without a clearcut differentiation on etiologic or pathogenic grounds. A considerable number of unrelated diseases, each with a distinctly different etiology, have now been observed in which there are hemorrhagic symptoms and a hematologic picture identical on the one hand with purpura haemorrhagica and on the other with Henoch-Schonlein's disease.

In the thrombocytopenic group it has become increasingly evident that so-called essential purpura haemorrhagica is not a specific clinical entity but rather a miscellany of heterogeneous diseases in which purpuric manifestations, a lower platelet count and other abnormalities of the blood constitute common incidental features. The scope of this diagnosis has become greatly narrowed by the recognition of the picture of purpura haemorrhagica in various leukemias, aplastic anemia and other blood dyscrasias, in a variety of intoxications, such as with benzene or arsphenamine, and in a number of infectious diseases, such as typhoid. That even the remainder of the conditions still left in this narrowed category of idiopathic thrombocytopenic purpura do not comprise a uniform entity is suggested among other things by the variable results of splenectomy, which in some instances effects a brilliant cure while in other cases of apparently the same disease it is totally ineffective. Furthermore, even in instances of cure following splenectomy, the mechanism of relief seems to differ in the various cases, in some this operation is followed by a restoration of the platelets to a normal number, and in others the amelioration of symptoms is effected without any alteration in the quantity of these elements. This suggests, at least, that the mechanism at fault is different in these two types of purpura.

In the cases which we have presented the condition bore all the characteristics of essential purpura haemorrhagica of the acute fatal variety. None of the known causes of symptomatic thrombocytopenic purpura were applicable in these cases. In each of the three cases the clinical impression was that of a general infection. In one case the presence of lobar pneumonia could account for the septic nature of the disease. In two cases a provisional diagnosis of subacute bacterial

endocarditis was made. One or more blood cultures were made in each case, but all cultures proved sterile. The course of the disease was rapidly downhill. Conservative measures were ineffectual. Transfusions hardly raised the hemoglobin or erythrocyte count at all, and the downward progress of the disease was not even temporarily stemmed. In the first two cases, despite repeated transfusions, the hemoglobin value dropped to 18 per cent and 30 per cent, respectively. Neither splenectomy nor double ligation of the splenic artery was of any avail.

The occurrence of icterus in two of the three cases was an unusual feature. In case 1 this appeared to be associated with a rapid destruction of the erythrocytes. The increased excretion of urobilin in the urine, especially after the transfusion, also points in that direction. One explanation for the icterus in these cases is the possible existence of hepatic damage, which has also been invoked as a partial explanation for the hemorrhagic symptoms in certain cases of purpura of toxic and infectious origin. In the three cases herein reported the liver was somewhat enlarged and showed cloudy swelling and granular and fatty degeneration. These alterations were hardly specific or severe enough to be significant, but the frequent meagerness of the anatomic changes even in cases of definite hepatic disturbance is well known. In the explanation of the jaundice in case 3 consideration must be given to the presence of a complicating lobar pneumonia, which has been associated with jaundice in 6.6 per cent of 635 cases in this hospital.<sup>10</sup> Its occurrence in such cases is not clear but has been ascribed to the decreased hepatic function in the presence of an increased formation of bilirubin.<sup>11</sup> But, as in the first case, in which pneumonia was not present, the icterus may have occurred as part of the general disease which produced the remaining symptoms.

Pathologically, there was nonbacterial thrombotic valvular endocarditis in all three cases, these having been selected from forty-seven cases of nonbacterial thrombotic endocarditis of various origins because of the association with thrombocytopenic purpura. In two of the three cases there was organizing pericarditis. The spleen was considerably enlarged in two cases and moderately enlarged in the third case. All the patients presented features usually associated with a general infectious disease. A detailed description of thrombotic endocarditis and a discussion of its classification and pathogenesis formed the basis of a previous report.<sup>1</sup> At present it will suffice to make a few brief comments regarding the thrombotic endocarditis in the cases under discussion. The vegetations did not belong to the bacterial group, which includes subacute bacterial endocarditis. There were no bacteria in the vegetations,

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10 King, F. Personal communication to the authors.

11 Rich, A. R. *Bull. Johns Hopkins Hosp.* **47**: 338-377, 1930.

no ulceration, no perforation of the valves or rupture of the chordae tendineae and no embolic glomerular lesions such as are generally present in subacute bacterial endocarditis. Grossly, the vegetations which were situated on the mitral or on the mitral and aortic valves did not have the characteristic warty appearance and, more particularly, were considerably larger than the vegetations usually observed in rheumatic fever. Microscopically, there were no interstitial valvulitis, no Aschoff bodies in the myocardium and no MacCallum lesions in the auricular endocardium. The vegetations consisted of a partially organized blood platelet thrombus with little or no reaction in the valve substance. In short, there was no evidence to suggest that the vegetations were part of an acute rheumatic endocarditis. In two cases there was moderate and in one case slight evidence of healed rheumatic infection. We have elsewhere indicated the frequency and importance of valvular damage due to such infection in predisposing to terminal nonbacterial thrombotic deposits<sup>1</sup>.

In addition to the various features mentioned, there were widespread unusual vascular lesions in one case, which consisted essentially of granular plugs in the capillaries and precapillary vessels. These plugs were undergoing organization and hyalinization. Their margins appeared endothelialized, and recanalization of the obstructed vessels occurred. As stated before, a detailed description and discussion of the pathogenesis of these lesions will be presented by Baehr, Klemperer and Schiffrin<sup>6</sup> in the *Transactions of the Association of American Physicians* for 1936. In their report there is presented case 1 of this series together with three other cases of acute febrile anemia with thrombocytopenic purpura and diffuse blood platelet thrombosis of vessels. As in the latter three cases endocarditis was not evident, it appears that endocarditis is not an essential part of the disease. Furthermore, as these authors suggest, identical cases may occur without anatomically visible vascular lesions, the reduction in the blood platelet count being due not to intravascular thrombosis but to extravascular exudation through capillaries with damaged walls. Thus, the brother of one patient (case 1) died after apparently identical acute thrombocytopenic purpura, but no vascular lesions were discovered post mortem. Whether this explanation may be invoked for the last two cases in our series, in which there were no significant vascular lesions, or whether the lesions represented a considerably milder form of vascular injury it is impossible to state. However, it is of interest to note that our three cases are the only ones of eleven cases of thrombocytopenic purpura in which autopsy was performed in our hospital during the last thirteen years in which there was associated nonbacterial thrombotic endocarditis.

There is some question as to the primary importance of thrombocytopenia in these cases. Both the reduction in the blood platelet count and the hemorrhagic symptoms may have been manifestations of a general disease which injured the blood vessels and which also produced febrile anemia, thrombotic endocarditis, pericarditis and sometimes visible vascular abnormalities. Certainly the therapeutic failure of splenectomy and the abundance of megakaryocytes in the bone marrow preclude the usual type of purpura haemorrhagica resulting from the excessive splenic destruction of blood platelets or the inadequate formation of platelets in the bone marrow.

The primary importance of a reduction in the number of blood platelets in the causation of purpura has been especially stressed by Frank<sup>12</sup> and his followers. A good deal of evidence, however, has accumulated which casts doubt on the predominant significance of the reduction of these elements even in cases of thrombocytopenic purpura. That cure follows splenectomy even when a low platelet level persists after operation has already been mentioned (Kaznelson,<sup>13</sup> Ehrenberg,<sup>14</sup> Cori,<sup>15</sup> and Kleeblatt<sup>16</sup>). While the favorable results following splenectomy have generally been ascribed to a diminished destruction of platelets, whether directly in the spleen (Kaznelson) or by removal of the toxic effect of the spleen on the bone marrow (Frank), Bedson<sup>17</sup> stated that he believed on experimental grounds that the effectiveness of splenectomy is due to the increase in the capillary resistance following this procedure. Failures of correlation between the diminution in the number of blood platelets and the hemorrhagic symptoms have been reported by Katsch,<sup>18</sup> Stahl,<sup>19</sup> Sternberg,<sup>20</sup> Gram,<sup>21</sup> Weil<sup>22</sup> and others. Experimental thrombopenia in animals has been produced without purpura and even without a prolonged bleeding time (Ledingham<sup>23</sup> and Roskam<sup>24</sup>). In their latest classification of hemorrhagic diseases,

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12 Frank, E. *Neue deutsche Klin* **4** 395-437, 1930

13 Kaznelson, P. *Deutsches Arch f klin Med* **128** 119-130, 1918

14 Ehrenberg, C. *Monatschr f Geburtsh u Gynak* **51** 99-117, 1920

15 Cori, G. *Ztschr f klin Med* **94** 356-369, 1922

16 Kleeblatt, F. *Beitr z klin Chir* **120** 412-426, 1920

17 Bedson, S. P. *J Path & Bact* **25** 94-104, 1922

18 Katsch, G. *Munchen med Wchnschr* **65** 897-900, 1918

19 Stahl, R. *Deutsches Arch f klin Med* **132** 53-68, 1920

20 Sternberg, F. *Wien Arch f inn Med* **3** 433-452, 1922

21 Gram, H. C. On the Platelet Count and Bleeding Time in Diseases of the Blood, *Arch Int Med* **25** 325-332 (March) 1920

22 Weil, P. Emile. *Rev de med, Paris* **37** 81-102, 1920

23 Ledingham, quoted by Morawitz, P. *Verhandl d deutsch path Gesellsch* **25** 32-45, 1930

24 Roskam, J. *Sang* **3** 497-528, 1929



Pfaundler<sup>25</sup> and Naegeli<sup>26</sup> failed to divide them into the thrombocytopenic and the athrombocytopenic forms, and Morawitz<sup>27</sup> stated that hemorrhagic diatheses do not exist without vascular changes

In anemia leukemia, avitaminosis, sepsis and various infectious diseases hemorrhagic symptoms may occur with a thrombocytopenic blood picture. But similar purpuric manifestations occur in the identical diseases without any diminution in the platelet count. This suggests the possibility that in these diseases thrombopenia played no part or was only accessory to some other factor or factors in the causation of bleeding. This other factor may lie in the vascular damage which occurs in these diseases, as indicated by various anatomic studies

In leukemia, in addition to the changes in the bone marrow, Naegeli has described infiltration and destruction of the vessel wall by leukemic infiltrations. In cases of meningococcemia histologic studies, especially by L. Pick,<sup>28</sup> have shown that the hemorrhages were due to bacterial emboli with direct destruction and inflammation of the wall of the vessel. In other infections with purpura M. B. Schmidt<sup>29</sup> sometimes noted irritative phenomena of the veins and capillaries, especially in the form of enlargement and proliferation of cells with nonbacterial granular thrombi. Herzog and Roscher<sup>30</sup> observed that in typhoid the hemorrhages were due to embolic involvement of the small vessels which were plugged with typhoid bacilli. In subacute bacterial endocarditis in which purpura may be present with or without thrombopenia, the hemorrhages may be due to emboli, to toxic arteritis (as described by Merklen and Wolf<sup>31</sup>) or to local closure by intimal proliferation. Reference has already been made to the four cases comprising a series which will form the basis of the report by Baehr, Klemperer and Schiffin,<sup>6</sup> in which these authors attribute the thrombopenia to vascular damage followed by intravascular thrombosis or extravascular exudation of blood platelets

The condition in the cases here presented may be related to the larger group interpreted by Baehr<sup>32</sup> as the expression of a system disease affecting the capillaries and finer ramifications of the vascular tree and to the lupus erythematosus recently discussed by Baehr, Klemperer

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25 Pfaundler, M., and von Seht, L. *Ztschr. f. Kinderh.* **29** 225-380, 1919

26 Naegeli, O. *Blutkrankheiten und Blutdiagnostik*, ed. 5, Berlin, Julius Springer, 1931

27 Morawitz, P. *Verhandl. d. deutsch. path. Gesellsch.* **25** 10-32, 1930

28 Pick, L. *Deutsche med. Wchnschr.* **42** 994-998, 1916

29 Schmidt, M. B. *Verhandl. d. deutsch. path. Gesellsch.* **25** 10-32, 1930

30 Herzog, F., and Roscher, A. *Virchows Arch. f. path. Anat.* **233** 347-371, 1921

31 Merklen, P., and Wolf, M. *Presse med.* **36** 97-100, 1928

32 Baehr, George. *Tr. A. Am. Physicians* **46** 87-95, 1931

and Schiff<sup>11</sup> This endothelotoxic effect may in itself be adequate to explain the purpuric manifestations The relationship of the reduced number of blood platelets to this generalized disease must remain hypothetical In some cases, however, such thrombopenia may result from blood platelet thrombosis associated with vascular damage as suggested by these authors

#### SUMMARY

In a previous study on indeterminate forms of endocarditis, cases of nonbacterial thrombotic endocarditis were described and classified In certain groups there were several clinical and pathologic features in common

This report deals with one of these groups, comprising three cases, in which there were clinical features of acute fulminating (thrombocytopenic) purpura haemorrhagica

Fever, purpura, epistaxis, bleeding of the gums, severe anemia, a low blood platelet count, poor clot retraction, a prolonged bleeding time and a rapid downward course were the dominant features In each case observers considered the probability of a general infection, but blood cultures were sterile

At necropsy, in addition to nonbacterial thrombotic endocarditis, each of the three patients showed an acute splenic tumor, in two cases there was organizing pericarditis and in one case widespread vascular lesions

The possible relationship of an infectious process producing vascular damage and the purpuric phenomena are discussed

# NONBACTERIAL THROMBOTIC ENDOCARDITIS

ASSOCIATED WITH PROLONGED FEVER, ARTHRITIS, INFLAMMATION  
OF SEROUS MEMBRANES AND WIDESPREAD VASCULAR LESIONS

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In a previous report<sup>1</sup> several groups of cases were described and classified under the general designation of nonbacterial thrombotic endocarditis. This form of endocarditis is characterized by thrombotic vegetations, often of unusual size and appearance, with a minimum of reaction in the valve itself. It differs from the variety due to acute rheumatic infection and from the type described by Libman and Sacks as "atypical verrucous endocarditis"<sup>2</sup>. Among the several subdivisions of nonbacterial thrombotic endocarditis, two appear to have certain clinical and pathologic features in common. One of these subdivisions (reported on elsewhere<sup>3</sup>) was represented by a group of three cases characterized by acute (thrombocytopenic) purpura haemorrhagica, nonbacterial thrombotic endocarditis and vascular lesions which were widespread in one case and considerably milder in the other two cases.

The present communication is a detailed account of another group of cases in which prolonged fever, arthritis, inflammation of the serous membranes and alterations of the blood vessels were prominent features. This group comprised four cases, all in young women. The onset was marked by acute polyarthritis simulating rheumatic fever. There was evidence of involvement of the pleura and pericardium with signs of fluid in these serous cavities. Clinical evidence of endocardial involvement was absent or minimal. There was persistent fever. Blood cultures were sterile. There were accompanying symptoms of nephritis without any evidence of renal insufficiency, except in a case in which

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From the Medical Services and the Laboratories of the Mount Sinai Hospital.  
Aided by grants from the Lucius N. Littauer and Walter W. Naumburg Funds.

1 Gross, Louis, and Friedberg, C. K. Nonbacterial Thrombotic Endocarditis: Classification and General Description, *Arch. Int. Med.*, this issue, p. 620.

2 Libman, E., and Sacks, B. A Hitherto Undescribed Form of Valvular and Mural Endocarditis, *Arch. Int. Med.* **33**: 701-737 (June) 1924.

3 Friedberg, C. K., and Gross, Louis. Nonbacterial Thrombotic Endocarditis Associated with Acute Thrombocytopenic Purpura, *Arch. Int. Med.*, this issue, p. 641.

a moderate degree of renal insufficiency resulted from severe vascular lesions in the kidney. The course was subacute and progressive. Ascites developed toward the end and was discovered clinically or post mortem. Cardiac insufficiency was not a significant clinical feature. Death occurred as a result of cachexia or with symptoms of cerebral or pulmonary involvement. The arthritis differed in some respects from that in rheumatic fever and went on to marked deformity in two of the four cases. Postmortem examination revealed primarily subacute polyserositis, nonbacterial thrombotic endocarditis and vascular lesions of varying degrees of severity.

#### REPORT OF CASES

**CASE 1**—I. G., a 24 year old West Indian Negress, was first admitted to the Mount Sinai Hospital on Feb. 5, 1929, where she remained until April 23, 1930. She was in the City Hospital from May 26, 1930, until May 11, 1931, and in the Mount Sinai Hospital again from Sept. 2, 1931, until Jan. 21, 1932, in the service of Dr. B. S. Oppenheimer.

**History**—When this patient was first admitted to the Mount Sinai Hospital she complained of painful swollen joints, fever and sore throat for one month. Her family history did not include tuberculosis or rheumatic fever. Her past history was irrelevant, she had not suffered from rheumatic fever, sore throat, chorea, arthritis or scarlet fever. For the past year there had been various symptoms, but these had not been severe enough to interfere with her work. She had lost 15 pounds (6.8 Kg.) and had night sweats, occasional palpitation on exertion and a poor appetite. About a month preceding her admission to the hospital pain, swelling and redness developed in the right elbow, then in the left elbow and then in the wrists and ankles, the pains in one joint subsiding with the involvement of the next joint. Associated with these symptoms were a temperature as high as 102 F., sweating and a sense of chilliness. For two weeks the throat had been sore. She had been confined to bed for one month.

**Examination**—The patient was acutely ill. The teeth were carious. There were enlarged submental and anterior cervical lymph nodes. The apical impulse was in the fifth interspace well within the left mammary line. There was a short, soft, blowing systolic murmur localized in the apical region. The second pulmonary sound was louder than the second aortic sound. The abdomen was essentially normal. There were tender swellings involving the interphalangeal joints of the ring and index fingers of the right hand. The right wrist was tender and painful on motion. There was some swelling of both knees and difficulty in extending them. The right ankle also was tender. On the dorsa of both hands there were soft, fluctuant swellings about the size of a walnut. These were probably due to the accumulation of synovial fluid. Vaginal examination revealed only profuse leukorrhea. The temperature at the time of the patient's admission was 103.2 F. The pulse rate was between 110 and 120 per minute. The blood pressure was 96 systolic and 50 diastolic. The blood count showed 70 per cent hemoglobin, 10,200 leukocytes, 80 per cent polymorphonuclears, 12 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils. Urethral and cervical smears did not show gonococci. The sedimentation time was nineteen minutes.

A tentative diagnosis of acute rheumatic fever or acute infectious arthritis was made.

*Course*—For sixty-two weeks the patient was almost continuously febrile. The temperature was generally between 100 and 103 F, occasionally reaching 104 F. Several times there was an afebrile interval of about a week. There were frequent recurrences of migrating arthritis, with redness, heat and swelling of the larger joints of both upper and lower extremities as well as of the interphalangeal joints. Occasionally there was a correlation between the involvement of a new joint and the sudden elevation of temperature. By the ninth month of illness persistent deformities had developed, consisting of spindle-shaped swellings of the joints of the fingers of both hands (fig 1).

Despite a variety of abnormalities of the heart, there was never any certainty as to the presence of a valvular lesion. Throughout the period considered, there was always a short systolic murmur limited to the apex of the heart, and the second pulmonic sound was accentuated. One observer described a presystolic murmur, and another believed there was organic mitral disease, because of a short murmur he heard late in diastole. These signs were not confirmed by most of the other observers. In the third week there were definite pericardial and pleural rubs. In the fourth week there was clinical and roentgen evidence of pericardial

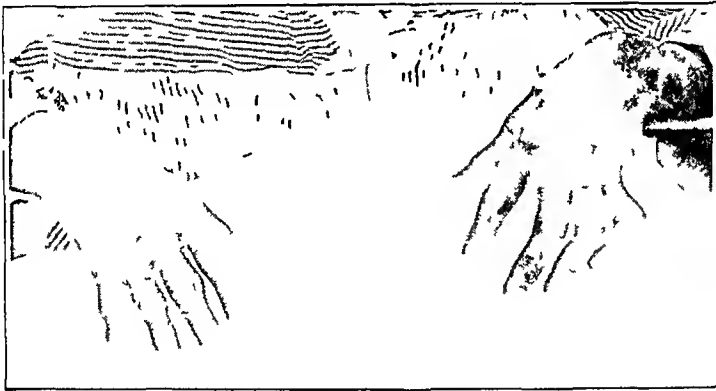


Fig 1—Proliferative arthritis of the joints of the hands of a patient with prolonged fever, inflammation of the serous membranes, vascular lesions and non-bacterial thrombotic endocarditis. Note the spindle-shaped joints of the right hand and the deformities with ankylosis of the joints of the left hand.

effusion. Repeated electrocardiographic examinations revealed the following: slight left axis deviation, notching of the QRS complexes, changes in the RT transitions in the second and third leads, a broad and notched P wave in leads I and II, and inversion and coving of  $T_1$  and  $T_2$ . The PR interval was 0.2 second. The changes were interpreted at various examinations as indicating myocardial damage, a poorly functioning myocardium or recent coronary occlusion. A roentgenogram of the heart was suggestive only of mitralization.

Shortly after admission to the hospital the patient showed pulmonary signs which persisted throughout her hospital stay. At first dulness and diminished bronchovesicular breathing were noted at the bases of both lungs posteriorly. On roentgen examination small pleural effusions were found at the bases. Repeated pleural taps yielded only 30 cc of fluid containing 1,600 cells per cubic millimeter, almost entirely lymphocytes. These signs persisted, and in addition there were many medium moist râles over the same region. Repeated roentgen examinations were interpreted as showing the presence of unresolved pneumonia. There was only a slight cough and little sputum, which did not show tubercle bacilli or other

significant bacteria. Nevertheless tuberculosis was considered as a possible diagnosis.

Wassermann tests were all reported as 4 plus. Treatment with arsphenamine, iodides and bismuth did not alter the result. There was no clinical evidence of syphilis except generalized adenopathy, which was more marked for one week after the patient had been in the hospital for two months.

The urine at the time of the patient's admission to the hospital was normal, but in the ninth month of illness albuminuria developed, and there were many casts and red blood cells present. The blood urea content and various tests made of renal function were normal. During this period transient pretibial edema and some puffiness of the face were noted. The blood pressure was never elevated. The fundi were always normal. Roentgenograms of the various joints showed swelling of the soft parts and some atrophy. The white blood cell count was variable, sometimes rising to 30,000, with 90 per cent polymorphonuclears. On the other hand, there were occasions when, despite a high temperature and pulmonary involvement, there was no leukocytosis. The hemoglobin value gradually dropped to 55 per cent. Six cultures of the blood, aerobic and anaerobic, showed negative results. Similar cultures of the pleural fluid were likewise sterile. Various agglutination tests of the blood and cultures of urine as well as inoculation of guinea-pigs with the urine gave negative results.

At the conclusion of more than a year's continuous observation the patient left the ward of the hospital still febrile, the symptoms unchanged, to be observed further in the medical outpatient department. It was remarkable that despite the high temperature, the patient was fairly comfortable, except for recurrent articular pains. The clinical condition was considered as undiagnosed, although there were several possibilities under consideration.

During the time of observation in the outpatient department the patient showed symptoms and objective signs, but she refused to return to the hospital ward. In May 1930 she was admitted to the City Hospital, Welfare Island, where she was observed for one year, without any significant change in the clinical course. She was finally discharged, still febrile, the condition undiagnosed. She was again observed in the outpatient department, and she continued to have fever and suffered attacks of dyspnea and precordial pain. After a severe attack of dyspnea and precordial pain she was induced to reenter the hospital on Sept 2, 1931.

Since her previous discharge the patient had lost 17 pounds (7.7 Kg) in weight and had become exceedingly weak, so that she was incapable of any work. Frequently, especially after eating, she would experience epigastric distress and precordial pain, accompanied with dyspnea, orthopnea and palpitation, lasting for a few minutes. She frequently felt as though she were dying during these attacks. She still suffered generalized pains in "all her bones" and in many of the joints, all of which had become stiff. The joints of the hands were deformed.

On examination she appeared chronically ill, emaciated, weak and orthopneic. The eyelids were puffy. There was a perforation of the septum of the nose. Submaxillary adenopathy was present. The lungs revealed dulness at both bases, with diminution of the breath sounds and many medium moist râles on inspiration. The heart was enlarged both to the right and to the left, the apex being in the sixth interspace in the anterior axillary line. There were no murmurs. There was a presystolic gallop rhythm, especially marked in the third interspace to the left of the sternum. The blood pressure was 130 systolic and 80 diastolic. The abdomen was distended but otherwise was normal. The hands showed atrophy of the dorsa, with retraction of the intermetatarsal spaces and flexion contracture of the fingers. The fingers could not be extended beyond an angle of 120 degrees.

Thickening and deformity of the interphalangeal joints were marked. Besides the presence of syphilis the patient was considered most likely to have chronic rheumatic fever with chronic rheumatic myocarditis and chronic pneumonitis or an unusual form of infectious arthritis with arthritis deformans.

The blood count showed 66 per cent hemoglobin, 4,850,000 red blood cells, 10,000 leukocytes and 84 per cent polymorphonuclears. The urine showed albumin, red and white blood cells and casts, but tests of function showed no evidence of renal impairment. Roentgenograms of the joints showed atrophy of the bones and narrowing of the spaces, with areas of erosion. Roentgenograms of the ribs showed erosion of the fifth, sixth and seventh ribs on the right side. Roentgenograms of the lungs showed infiltration at the bases, as on the previous examinations.

One month after the patient's admission to the hospital ascites appeared for the first time. Paracentesis yielded 700 cc of straw-colored fluid with a specific gravity of 1.008 and 300 cells per cubic millimeter, with 80 per cent lymphocytes and 20 per cent large mononuclear cells. Thereafter, fluid reaccumulated rapidly, and the abdomen was repeatedly tapped, several liters of fluid being removed on each occasion. Two weeks before the patient's death a diastolic murmur was noted in the third interspace on the left side. After four and one-half months of progressive emaciation and continued fever, the patient died, probably as a result of toxemia and cachexia.

*Postmortem Examination*—The diagnosis was polyserositis (chronic adhesive pericarditis, bilateral adhesive pleuritis, perihepatitis, perisplenitis and peritonitis), anasarca, nonbacterial thrombotic endocarditis of the pulmonic and aortic valves, chronic interstitial pneumonitis, pulmonary emphysema and arterial sclerosis, degenerative encephalopathy, synovitis, osteoporosis of the fifth, sixth and seventh ribs of the right side and of the sixth rib on the left side, chronic passive congestion of the liver, kidneys, lungs and spleen, brown atrophy of the myocardium with focal fibrosis, and hemosiderosis of the pancreas.

There was marked emaciation. Scars of repeated paracentesis were present. The abdomen was protuberant, the umbilicus protruding. The third, fourth and fifth fingers of the left hand were in palmar and phalangeal flexion. There was slight edema of the lower extremities. Considerable ascites was noted. There were thickened adhesions binding the liver and spleen to the diaphragm, gallbladder and colon. The peritoneum was thickened. The liver was small and firm and was covered by numerous icy gray-white edematous adhesions over the diaphragmatic surface resembling the zuckergussleber. The liver had a nutmeg appearance, owing to passive congestion. The spleen had a thickened, edematous capsule and was purplish red on section. The gastro-intestinal tract showed passive congestion. The pancreas showed hemosiderosis. The pleural cavities were sealed by adhesions, and there were similar adhesions between the pleura, the pericardium and the mediastinum. The fifth, sixth and seventh ribs were adherent to the scapula. The lungs were atelectatic and showed markedly thickened septums, which appeared as an irregular network of grayish white streaks.

The pericardium was completely adherent. The heart was of normal size. On the closure line of the posterior cusp of the mitral valve was superimposed a pyramidal ridge, on which was a row of slightly raised yellowish verrucae the size of a pinhead. A similar row of verrucae was present on the aortic cusp of the same valve. At the commissure between the right and the left cusp of the aortic valve there was an unusual tawny gray, friable, rather massive conglomerate verrucous deposit, somewhat larger than a pea. A similar massive vegetation was present between the right and the posterior cusp of the pulmonary valve. The

myocardium showed some tigering and fibrosis. Examination of the right knee joint revealed edema of the capsular tissue. Synovia was removed for microscopic study.

Microscopically there was organizing pericarditis. Corresponding to the gross vegetations were some large blood platelet thrombi (fig 2) which were undergoing early organization at the bases and which were slightly endothelialized at the edges. There was no valvular reaction to the verrucae. The cusps and rings were apparently normal. No auricular lesion or Aschoff bodies were present. The smallest blood vessels in the myocardium showed thickening, intimal proliferation (fig 3), hyaline and granular plugs and recanalization. There was marked replacement fibrosis, probably secondary to vascular changes. There were many foci of lymphocytic infiltration.

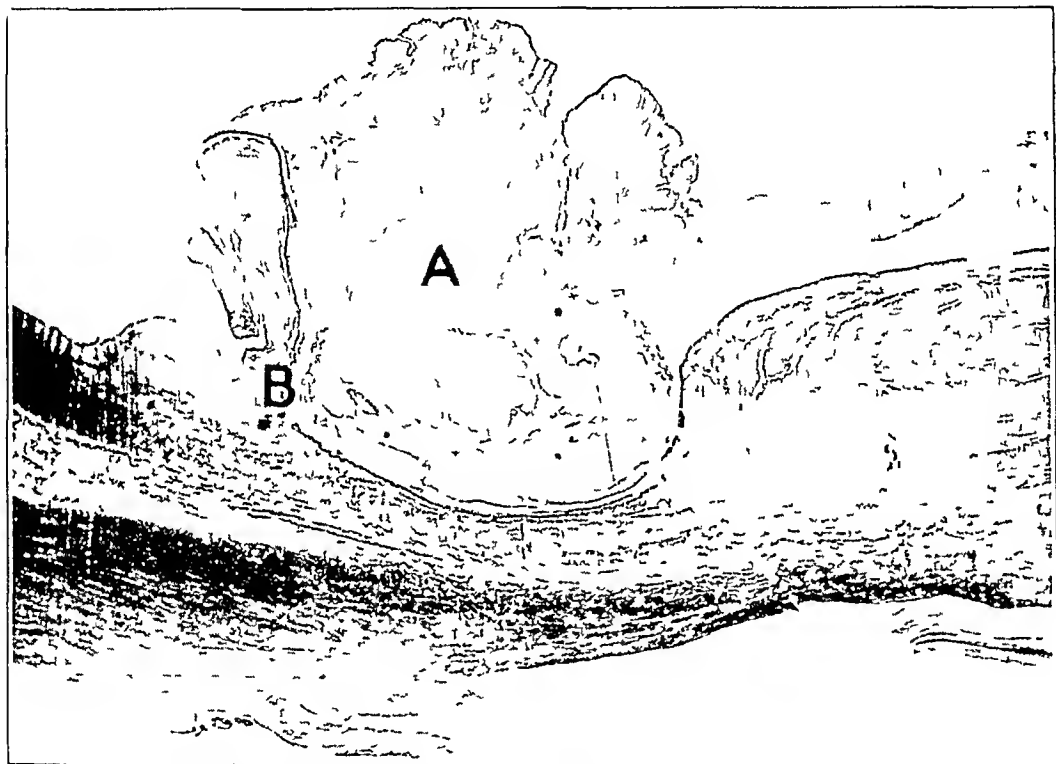


Fig 2—Nonbacterial thrombotic endocarditis of the aortic cusps. Weigert's elastic tissue stain and Van Gieson's connective tissue stain, low power. Section of the commissure of the aortic valve showing (A) a massive thrombus and (B) organization at the base of the thrombus. There is practically no inflammatory reaction in the cusp.

The kidney was cyanotic, and the glomeruli showed swelling and proliferation of endothelial and epithelial cells. Albumin could be seen in many of the capsular spaces. The blood vessels of the kidney showed only slight alteration. Sections of the synovial membrane showed loose and dense edematous connective tissue and fat. A large vein showed medial and adventitial infiltration with round cells and polymorphonuclear leukocytes and in one area degeneration of the media. There were other cellular infiltrations about smaller vessels.



*Comment*—The outstanding clinical features in this case were the prolonged febrile course (three years) with persistently sterile blood cultures, the onset with acute polyarthrititis, the development of deformities of the joints, particularly those of the fingers, and the presence of pleural and pericardial rubs, persistent physical signs and roentgen evidence of chronic pneumonitis, pleural effusion and possible pericardial effusion, recurrent ascites with little or no edema, questionable endocardial involvement, clinical symptoms of nephritis without elevation of the blood pressure and without impairment of the renal function, progressive emaciation and anemia

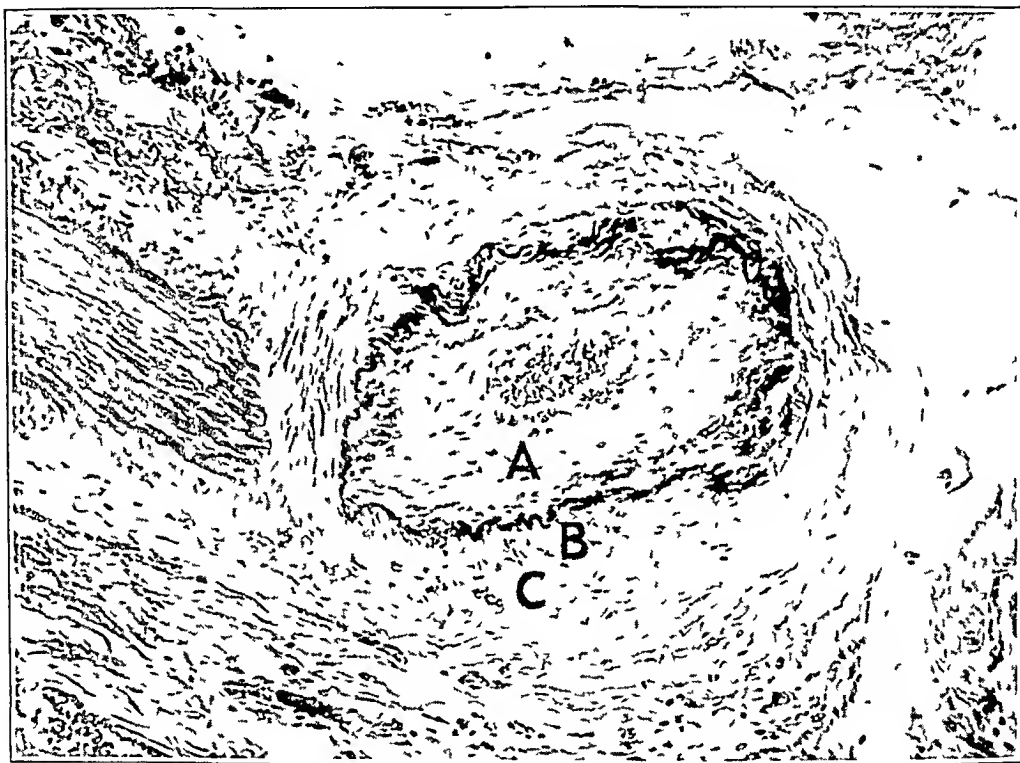


Fig 3—A vascular lesion in the posterior papillary muscle of the left ventricle of a patient 24 years old. Weigert's elastic tissue stain and Van Gieson's connective tissue stain, medium power. Section showing (A) marked intimal proliferation, (B) the media and (C) the adventitia.

Early in the course of the disease the striking migrating polyarthrititis and high temperature were suggestive of acute rheumatic fever, especially when associated with pericarditis and signs of pulmonary involvement. On two occasions small nodules were noted on the dorsum of the wrist and on the elbow, but biopsy of one of these nodules gave no confirmation of rheumatic infection, and no other nodules were seen at the sites commonly involved in rheumatic fever. Furthermore, the prolonged atypical course, the failure to respond to salicylates, the uncer-

tainty of endocardial involvement despite recurrent arthritis, the unusual pulmonary signs, the symptoms of nephritis and the development of spindle-shaped deformities of the joints of the fingers cast considerable doubt on the diagnosis of rheumatic fever.

Another consideration was some form of tuberculosis, in support of which were the long-standing pulmonary involvement with fever, symptoms of pleuritis and pericarditis, the adenopathy, the spindle-shaped joints, the positive reaction to tuberculin and the absence of leukocytosis during the major part of the febrile course. The articular involvement was interpreted as a form of arthritis in the course of tuberculosis (Poncet). Against the diagnosis of tuberculosis, however, was the basal location of the pulmonary signs, the absence of cough or sputum, the absence of bacilli in the sputum and the negative results of inoculations of guinea-pigs. Finally, because of the prolonged septic course, the absence of positive results of blood cultures, the involvement of numerous organs, the renal phenomena, the appearance of two subcutaneous nodules and the generally atypical course, some unusual condition like periaortitis nodosa was considered. The positive Wassermann reaction was believed to be a coincidental finding.

Postmortem examination revealed no evidence of tuberculosis or rheumatic fever. The outstanding change was widespread inflammation and adhesions of the various serous cavities and obliteration of the pleural and pericardial cavities. The adhesions over the liver gave it the characteristic *Zuckerguss* appearance. The heart revealed peculiar thrombotic verrucae of nonspecific character at the commissures of the aortic and pulmonary valves. The smaller arteries and veins of the myocardium likewise showed nonspecific alterations. Despite the renal symptoms, renal disease was slight.

CASE 2—E. E., a 48 year old woman, was admitted to the Mount Sinai Hospital, service of Dr. B. S. Oppenheimer, on Sept. 16, 1928, and died on November 16.

*History*—Three years before her admission to the hospital, this patient began to suffer from rheumatic symptoms, consisting of pain and swelling of the joints (fingers, wrists, knees, ankles) which persisted irregularly. Three months before her admission to the hospital a physician attended her for arthritis associated with fever, and at that time he heard a definite pericardial rub. Shortly afterward she seemed to suffer some cerebral episode with syncope and transient palsies of the cerebral nerves. She was taken to the Fordham Hospital, where she remained for four weeks with a temperature between 101 and 103 F., marked arthritis and progressive anemia. Since then she had suffered from frequent sore throats, weakness, shortness of breath, palpitation and occasional presternal pain. Her appetite had been poor, and she had lost weight.

*Examination*—The patient was a pale woman, somewhat orthopneic, who complained of weakness. There was slight exophthalmos, and the scleras were blue. At the bases of both lungs there were dulness on percussion, absent tactile

fremitus and diminished breath and voice sounds. The area of cardiac dulness was considerably increased, the apex being situated 10 cm to the left of the midline in the fifth interspace. The cardiac rate was 120 per minute. The first sound at the apex was snapping and was followed by a short systolic murmur. There was a rough systolic murmur over the pulmonic area, and the second sound here was accentuated and louder than the second aortic sound. The abdomen appeared tense, and the liver was palpable and somewhat enlarged. The abdominal reflexes were absent. There was incomplete extension of both elbow joints due to partial ankylosis. Tenderness and pain were noted on motion of both elbow joints. The right elbow was hot, red and swollen. The left wrist joint was painful. There was a Babinski reflex on the right. The temperature on admission was 104 F. The blood pressure was 106 systolic and 58 diastolic. The blood count showed 23 per cent hemoglobin, 1,530,000 erythrocytes, 11,900 leukocytes, 83.5 per cent polymorphonuclears, 14.5 per cent lymphocytes and 2 per cent monocytes. The Wassermann reaction of the blood was negative. The urine showed a trace of albumin, leukocytes and occasional granular casts. The urea nitrogen content of the blood was 17 mg per hundred cubic centimeters. The phenolsulfonphthalein test showed 20 per cent excretion in two hours.

The tentative diagnosis was chronic rheumatic cardiovalvular disease, subacute bacterial endocarditis, chronic infectious arthritis and severe secondary anemia, with intra-abdominal neoplasm to be ruled out.

*Course*—Despite the suggested diagnosis, the nature of the condition was still considered obscure after two weeks of observation. The course continued to be febrile, the temperature oscillating between 99 and 103 F. Repeated blood cultures remained sterile. On three different occasions white-centered petechiae were observed on the palpebral conjunctivae. Roentgen examinations made on several occasions showed small pleural effusion of the right side of the chest and of the left pleural cavity and once bilateral thickening of the pleura, without any other abnormality. The physical signs in the chest remained practically the same. Aspiration of the pleural cavities was nonproductive. Roentgen examination of the elbows, wrists, knees and ankles showed a moderate degree of hypertrophic arthritis. Electrocardiographic examination showed simple tachycardia and inversion of the T wave in the third lead. The patient finally died of anemia and cachexia. Despite the negative results of blood cultures and because of the febrile, septic course, the severity of the anemia and the white-centered petechiae, which were considered to be embolic, a diagnosis of subacute bacterial endocarditis was considered most likely, although the exact nature of the disorder remained obscure up to its termination.

*Postmortem Examination*—The diagnosis was subacute polyserositis, nonbacterial thrombotic endocarditis of the mitral and tricuspid valves, acute bronchitis, disseminated sclerosing encephalomalacia, acute splenic tumor, infarcts of the spleen, parenchymatous degeneration of the kidney and liver, diffuse endarteritis with thrombosis and recanalization and arthritis with deformity.

Pallor and emaciation were marked. The periarticular regions of the joints as well as the joints themselves were markedly swollen. The swelling was especially marked in the right knee, both elbows and both ankles. The cavity of the right knee joint had a markedly thickened, whitish glossy capsule and contained 25 cc of dirty yellow fluid. Microscopically, the inner surface of the joint cavity showed proliferation of the endothelium. It was covered in several places by fibrinoid material. Beneath this layer was cellular infiltration consisting of polymorphonuclear leukocytes, lymphocytes, mononuclear cells and occasional giant cells. The stroma was edematous and contained a few gram-positive cocci.

Both pleural cavities were practically obliterated by adhesions involving the visceral and parietal layers on all the surfaces of the lungs. The lungs themselves were practically normal. The bronchi were congested with a red frothy fluid and mucus. The heart and pericardium weighed 510 Gm. The pericardium presented a glossy whitish icing of adhesions. The parietal pericardium was intensely edematous and thickened about  $\frac{1}{2}$  inch (1.3 cm). It was extremely adherent throughout and was separated with difficulty from the thickened, edematous white visceral layer. The heart did not appear enlarged. On the mitral valve was an irregular, confluent row of yellow, friable granular vegetations the size of a pinhead, situated along the closure line but overhanging so as to reach to the free edge of the valve. Similar rows of vegetations were present on the tricuspid and aortic valves. There was no evidence of valvular deformity. Microscopic examination revealed blood platelet thrombi on the auricular surface of the mitral and tricuspid valves and on the ventricular surface of the aortic valves. The thrombi were partially vascularized and were undergoing organization. In the case of the aortic and tricuspid valves there was little or no reaction within the valve. In the mitral valve there was considerable cellular infiltration, including polymorphonuclear leukocytes, plasma cells and fibroblasts. There was slight evidence of necrosis. The appearance of the mitral valve bore some resemblance to that seen in atypical verrucous endocarditis. The ring of the mitral valve showed an inflammatory lesion suggestive of rheumatic fever. The lesion was rather more severe than that seen in atypical verrucous endocarditis. The rings of the aortic and tricuspid valves showed infiltration with mononuclear cells. There were no acute auricular lesions, Aschoff bodies or Bracht-Wachter lesions in the myocardium.

The peritoneal cavity contained about 300 cc of clear yellowish fluid. There was widespread involvement of all the intestinal loops by extensive thin dull white irregular adhesions. The liver was adherent throughout its entire peritoneal surface to the adjacent peritoneum. The spleen showed similar adhesions. The liver was congested and showed granular areas of degeneration. On microscopic examination there was an exudate of fibrin and leukocytes on Glisson's capsule with partial organization of the exudate. The spleen weighed 420 Gm and showed dull white patches resembling infarcts. Microscopically, there were wide areas of necrobiosis. The kidneys showed punctuate hemorrhages. The capsule stripped with difficulty. Microscopic examination showed marked perivascular infiltration with glia cells and pigment-laden gitter cells and gliosis in the region of blood vessels. The small arteries of the heart, lungs, pancreas, thyroid gland and spleen showed endothelial proliferation and hyaline and granular plugs (fig 4) with organization and recanalization.

*Comment*—The main features of this case were the prolonged febrile course (at least six months and probably longer) with sterile blood cultures, the long period of recurrent acute polyarthritis (three years) with deformities, the pericardial rub, the evidence of pleural effusions, the marked secondary anemia (23 per cent hemoglobin), the cerebral attack and the occasional white-centered petechiae in the conjunctivae. Because of the predominant arthritic symptoms at the onset, rheumatic fever was considered the likely diagnosis. However, the unusual course of the arthritis together with the development of deformities as well as the indefiniteness if not absence of valvular disease,

and the occurrence of white-centered petechiae made this diagnosis unlikely. With the appearance of petechiae and the continued septic course a diagnosis of subacute bacterial endocarditis was entertained, although the persistence of sterile blood cultures was disconcerting. Definite embolic phenomena other than the petechiae did not appear.

At postmortem examination there were subacute polyserositis with obliteration of the pleural and pericardial cavities and fluid and adhesions throughout the peritoneum. There was a slightly reactive nonrheumatic thrombotic endocarditis of the aortic and tricuspid valves. There were rather extensive vascular lesions consisting of endothelial proliferation

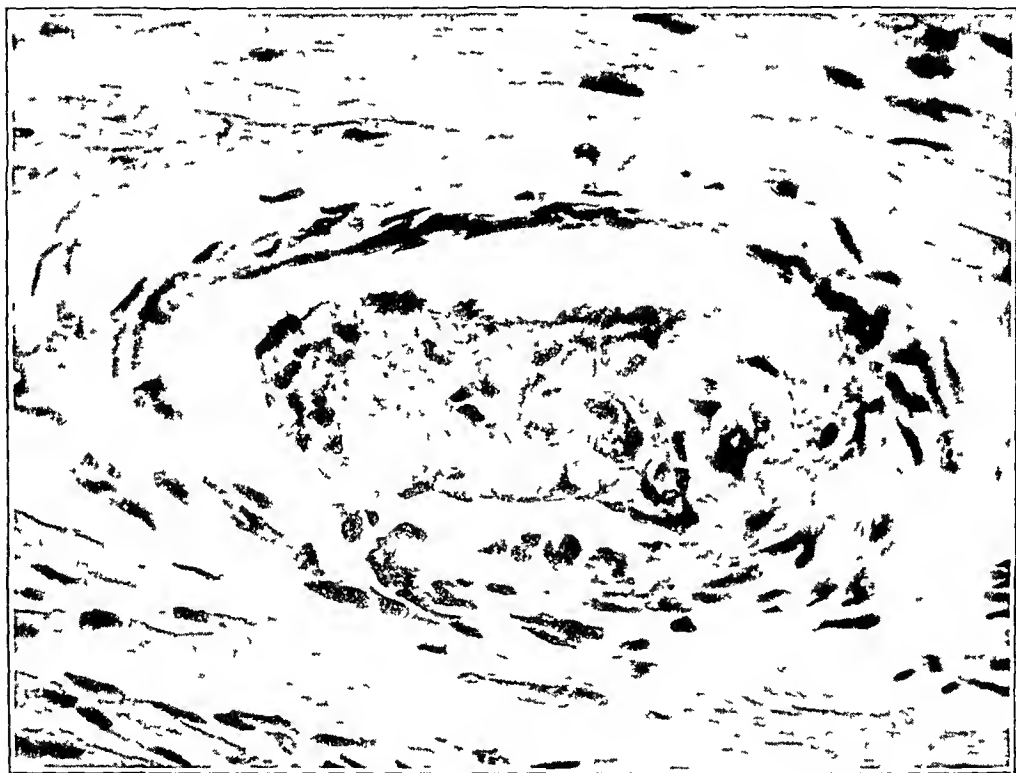


Fig. 4—A vascular lesion in the posterior papillary muscle of the left ventricle. Hematoxylin and eosin stain, high power. The small artery has a large granular plug projecting into its lumen. Note the attachment to the vessel wall at one end and the endothelialization of the free margins.

of the smallest arteries with hyaline and granular plugs and recanalization of the lumens. As in the first case, there was no definite evidence of either tuberculosis or a recent rheumatic infection. The ring lesion in the mitral valve was suggestive of rheumatic infection, but the absence of auricular lesions or of Aschoff bodies, the slightly reactive nonbacterial thrombotic endocarditis of the tricuspid and aortic valves and the atypical valvulitis of the mitral valve were opposed to a rheumatic etiology.

The possibility of an atypical verrucous endocarditis was not considered clinically in this case. Nevertheless, certain features were highly suggestive—the arthritis, the febrile course, the histology of a pericardial rub and the white-centered petechiae. Pathologically, the valvulitis in the mitral valve also suggested this diagnosis. There were, nevertheless, adequate reasons for not including the condition under that category. The history of arthritis (three years) was of much longer duration than is customary, and the development of ankylosis and deformities has not thus far been encountered in that disease. Other than isolated petechiae, there were none of the cutaneous lesions usually observed. Certain gross and microscopic features of atypical verrucous endocarditis were absent. Thus, there were no flat, spreading lesions and no tendency to involve the valvular pockets or the mural endocardium. Furthermore, there was little reaction in the valves which were the seat of vegetations. Renal lesions were absent. Finally, the involvement of serous membranes appeared to be more conspicuous and widespread than that reported in atypical verrucous endocarditis.

**CASE 3**—M. K., a 19 year old Irish waitress, was admitted to the Mount Sinai Hospital, in the service of Dr. G. Baehr, on June 4, 1928, and died on October 8.

*History*—Pain, redness and swelling of the ankles developed six months before the patient's admission to the hospital. The pain was severe enough to prevent her from walking and to require rest in bed for five weeks. During that time she suffered an attack of appendicitis and intestinal obstruction. The appendix was removed at another hospital. She felt well until two months before her admission to the Mount Sinai Hospital, when she began to suffer from breathlessness and palpitation. In the last three weeks fever, weakness and marked pallor had developed. She was treated by one physician for renal disorder, and by another for pleurisy with effusion. There was considerable loss of weight.

*Examination*—The patient was pale, poorly nourished, poorly developed and acutely ill. Dyspnea and orthopnea were moderate. The face was puffy, but there was no actual edema. The breath was urinous. The area of cardiac dullness was considerably enlarged to both the right and the left. The apical impulse could not be felt. The cardiac rate was rapid. There was a short systolic murmur over the precordium. There was dullness to percussion at the base of each lung below the angle of the scapula. At the base of the right lung there was absence or diminution of tactile fremitus, with egophony and absence of breath sounds. At the base of the left lung there was diminished tactile fremitus with egophony and diminished breath sounds. Over the upper portion of the right lung posteriorly there was bronchovesicular breathing with a few moist and crepitant râles and increased tactile fremitus. Over the upper portion of the left lung posteriorly there was bronchovesicular breathing but no râles. In the left axillary region there were bronchovesicular breathing and many moist râles. The abdomen was essentially normal. The blood pressure was 106 systolic and 60 diastolic. The urine had a low specific gravity and contained considerable albumin, hyaline and granular casts, leukocytes and occasional erythrocytes. The urea nitrogen content was 41 mg per hundred cubic centimeters of blood.

The tentative diagnosis was subacute glomerular nephritis with azotemia, bronchopneumonia, bilateral pleural effusion and pericardial effusion (?)

*Course*—There was persistent fever during the four months of the patient's stay in the hospital, with only brief remissions. The temperature ranged between 99 and 103 F, occasionally reaching 104 or 105 F. Two days after the patient's admission to the hospital a pericardial rub was heard, which persisted on and off for two weeks. The patient was then considered to have severe rheumatic disease affecting both the cardiac and the pulmonary structures. Roentgenograms confirmed the presence of pleural effusion and revealed some general enlargement of the cardiac outline. A definite pleural rub was heard on the left side two months after the patient's admission and at the base of both lungs shortly before her death. On one occasion seven weeks after her admission to the hospital there was a recurrent attack of arthritis with marked pain in both knees and ankles, accompanied with high fever and sore throat. A week later the right knee became swollen, red and tender, and shortly afterward there was similar involvement of the elbows and wrists. Electrocardiograms showed left axis deviation with an inverted T wave in the third lead and tachycardia (pulse rate of 116). Six blood cultures were made for aerobic and anaerobic organisms during the course of the illness, but they were all sterile. A systolic murmur was heard at various times during the course of the disease, but at no time was there any certainty as to the presence of valvular disease. There was considerable evidence of renal involvement. There was persistent albuminuria associated with hyaline and granular casts, leukocytes and red blood cells in the urine. The urea nitrogen content rose to 71 mg per hundred cubic centimeters of blood. The specific gravity of the urine was 1.016. A phenolsulfonphthalein test showed 20 per cent excretion in two hours. The albumin content of the blood was diminished to 2.5 per cent, with inversion of the albumin-globulin ration. In spite of transfusions there was progressive anemia, the hemoglobin content dropping to 34 per cent with 2,080,000 red blood cells per cubic millimeter of blood. There was never any leukocytosis, the leukocyte count at no time rising above 10,400 and generally remaining around 7,000 per cubic millimeter of blood. The sedimentation rate was rapid (eighteen minutes). The Wassermann test of the blood was negative. During the last month there was persistent abdominal pain which was difficult to control. Toward the end bilateral ulnar neuritis developed. Death occurred with pulmonary infarction and edema.

*Postmortem Examination*—The diagnosis was nonbacterial thrombotic endocarditis (mitral and aortic valves), necrotizing arteritis, chronic fibrous pericarditis and pleuritis, anasarca, subacute encephalopathy, pulmonary edema and bronchopneumonia, multiple anemic infarcts of the spleen, necrosis of the kidney and pancreas and fatty degeneration of the liver.

The body was that of a pale, poorly nourished young woman. Both pleural cavities contained several hundred cubic centimeters of straw-colored fluid. There were universal edematous adhesions between the parietal and visceral pleurae which were easily separated. There were large areas of bullous edema on the visceral pleura, especially on the diaphragmatic surface, where fibrous adhesions almost completely obliterated the pleural space. The diaphragm was edematous and thickened on its pleural aspect. On cut section the lung presented an edematous surface with deep red wedge-shaped areas of hemorrhage. Microscopic examination showed pulmonary edema and areas of bronchopneumonia.

The heart weighed 425 Gm. The parietal pericardium was adherent to the heart. It was markedly thickened and was stripped from the epicardium with

difficulty, revealing edematous pale fibrous strands between the surfaces. The pericardial space was represented by flat sacculated cavities. At the middle of the posterior cusp of the mitral valve, extending from the closure line to the free border, was a firm mushroom-shaped vegetation, about 1 cm at its widest extent, with a yellow, granular appearance. It was attached to the cusp by a narrow stalk. At the closure line of the anterior cusp there was a similar yellowish granular vegetation about 3 mm in width. The aortic valve presented two unusual vegetations situated at the commissures between the left and right and the left and posterior cusps, respectively (fig 5). They appeared like grayish yellow mounds of confluent smaller verrucae, with a rather friable surface and firm base. They were much larger than the vegetations in rheumatic disease, being about 8 mm in diameter. On the posterior mitral valve was a soft adherent vegetation about the size of a cherry pit, and along the closure line was a small row of pinpoint-sized translucent pinkish vegetations.



Fig 5—Nonbacterial thrombotic endocarditis of the aortic cusps. The arrow points to a large friable vegetation on the right-posterior commissure.

Microscopically there was organizing pericarditis. The verrucae consisted of blood platelet thrombi undergoing organization. In the mitral valve the thrombotic material was fused with superficial valvular substance which was undergoing eosinophilic change. There was evidence of only a slight reaction in the valve substance. The ring of the tricuspid valve showed a few polymorphonuclear leukocytes and lymphocytes, otherwise it was normal. There was no evidence of rheumatic disease noted in the auricular endocardium, in the valves or in the myocardium. There was a moderate amount of replacement fibrosis in the myocardium, probably secondary to widespread necrotizing arteritis (fig 6).

The peritoneal cavity contained 1 liter of clear straw-colored fluid. The kidneys showed marked congestion, yellow areas of infarction and flame-shaped hemorrhages throughout the cortex and medulla. Microscopic examination showed areas of hemorrhages and necrosis but only slight glomerular alterations. The liver showed an opaque, thickened, grayish capsule, passive congestion and fatty degeneration. The smaller arteries in the myocardium, kidneys, stomach and mes-



entry showed focal necroses with widespread inflammatory alterations. All the coats of the vessels were involved in the destructive lesion (necrotizing panarteritis).

*Comment*—The onset of the disease in this case was accompanied with fever and polyarthritis six months before the patient's admission to the hospital. As in the preceding cases there was a persistent febrile course with sterile blood cultures. Pleural and pericardial rubs were heard during her stay in the hospital. There were clinical and roentgen evidences of pleural effusions and considerable evidence of subacute

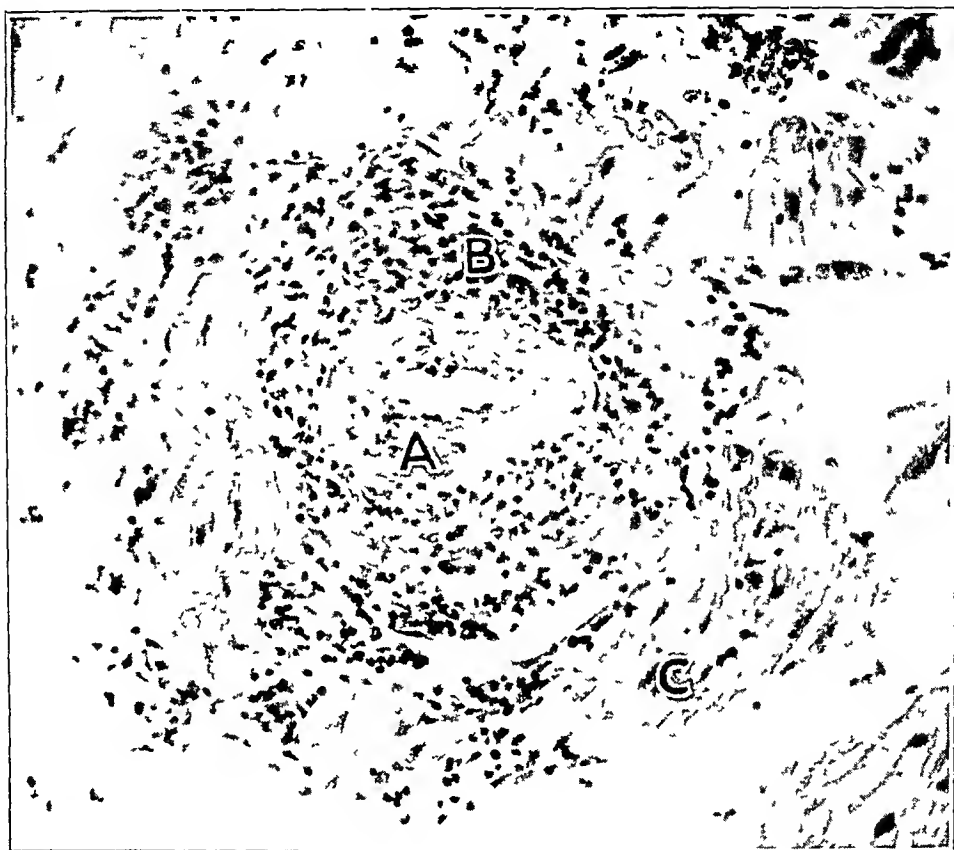


Fig 6—A vascular lesion in the left auricular myocardium. Hematoxylin and eosin stain, medium power. This section shows (A) necrosis, hyalinization and fusion of the intima and media, (B) perivascular leukocytic infiltration and (C) the myocardium.

nephritis with azotemia. Except for an inconstant systolic murmur, there was no reason to suspect valvular disease. Severe secondary anemia was present. Rheumatic fever was considered the most likely diagnosis, but the absence of valvular disease and the concomitant symptoms of nephritis confused the clinical picture. Postmortem examination revealed an organizing inflammatory lesion of the pericardium and pleura with fluid in the pleura, pericardium and peritoneum, nonbacterial thrombotic endocarditis, subacute encephalopathy and

diffuse vascular disease. The vascular disease in this case was more severe than in the preceding cases, showing necrosis and inflammation of all coats of the smaller arteries. The symptoms of nephritis were explained on the basis of vascular lesions in the kidneys.

CASE 4—B. S., a 21 year old Puerto Rican woman, was admitted to the Mount Sinai Hospital on Feb. 23, 1930, and discharged on May 19. On October 24 she was readmitted, in the service of Dr. Baehr, and died on November 1.

*History*—Pain had developed in the right lower quadrant of the abdomen one day before the patient's first admission to the hospital. There had been exposure to venereal disease a month before, followed by an increased vaginal discharge. On examination there was a roughened first cardiac sound with a blowing systolic murmur over the precordium. The blood pressure was 145 systolic and 100 diastolic. Marked tenderness was noted in the right loin, and fulness and tenderness were noted in the right vaginal fornix. There was a leukocytosis of 17,000, with 70 per cent polymorphonuclear leukocytes. Although the possibility of acute salpingitis or of visceral manifestation in Osler's disease was considered, a diagnosis of acute appendicitis appeared most likely. Operation was performed, and a normal appendix was removed. The fallopian tubes likewise were normal.

A review of the patient's history revealed that she had been suffering from polyarthritis for the past few months. The temperature was 101.6 F. on her admission to the hospital. The cardiac findings, the history of rheumatic pains and the fever combined to indicate a diagnosis of acute rheumatic fever. The temperature soon rose to 103.4 F. There were signs of pneumonia at the base of the right lung. The urine was of low specific gravity and contained albumin and casts. On the palmar and plantar aspects of the tips of the fingers and toes, respectively, there appeared diffuse erythema, telangiectasia and petechiae. The temperature remained between 103 and 104 F. for four and a half weeks and then gradually subsided. Blood cultures were sterile. One week after the patient's admission to the hospital there was a definite pericardial rub which persisted for four days. Then a pleural rub developed at the base of the right lung. At various times there were signs of fluid in both pleural cavities, especially on the right, but aspiration yielded none. There were physical signs of widespread infiltration of the entire right lung and of the lower lobe of the left lung. The specific gravity of the urine was 1.018. There was moderate secondary anemia (hemoglobin, 58 per cent, erythrocytes, 4,000,000 per cubic millimeter). There was recurrent arthritis of both knees and of the left elbow one week after the patient's admission to the hospital. The Pirquet test showed a negative result. The Wassermann test of the blood was negative. An electrocardiogram revealed inversion of the T wave in the third lead and a low T wave in the first and second leads. The record was interpreted as indicating poor myocardial function. Certain observers heard a diastolic murmur at the apex of the heart. With subsidence of the fever and the regression of the pulmonary signs, the patient was considered well enough to be sent to the country for convalescent care.

After discharge from the hospital the patient occasionally felt feverish and suffered from night sweats. Her strength did not increase. Pain developed in the left side of the chest and was aggravated by respiration. She had a severe chill on the day before her readmission to the hospital. She appeared chronically ill, the eyelids were puffy and there was pallor of the mucous membranes. There was a small exudate in the right fundus of the eye. The heart rate was irregular and rapid. There was no apparent cardiac enlargement. There was a long sys-

toxic murmur over the pulmonic area. The blood pressure was 126 systolic and 92 diastolic. There was a thick purulent vaginal discharge. Smears of material from the cervix, vagina and urethra showed no gonococci. The temperature was 101.8 F. The hemoglobin value was 54 per cent. There was marked asthenia. The patient was considered to be suffering from subacute bacterial endocarditis in the bacteria-free stage or from generalized tuberculosis.

The patient's condition became progressively worse. Three days after her second admission to the hospital she appeared to be in a state of vasomotor shock, for which there was no obvious cause. The possibility of cerebral embolus or of long-standing toxemia was considered. Persistent vomiting with alkalosis and tetany due to the vomiting developed, and the patient died one day later.

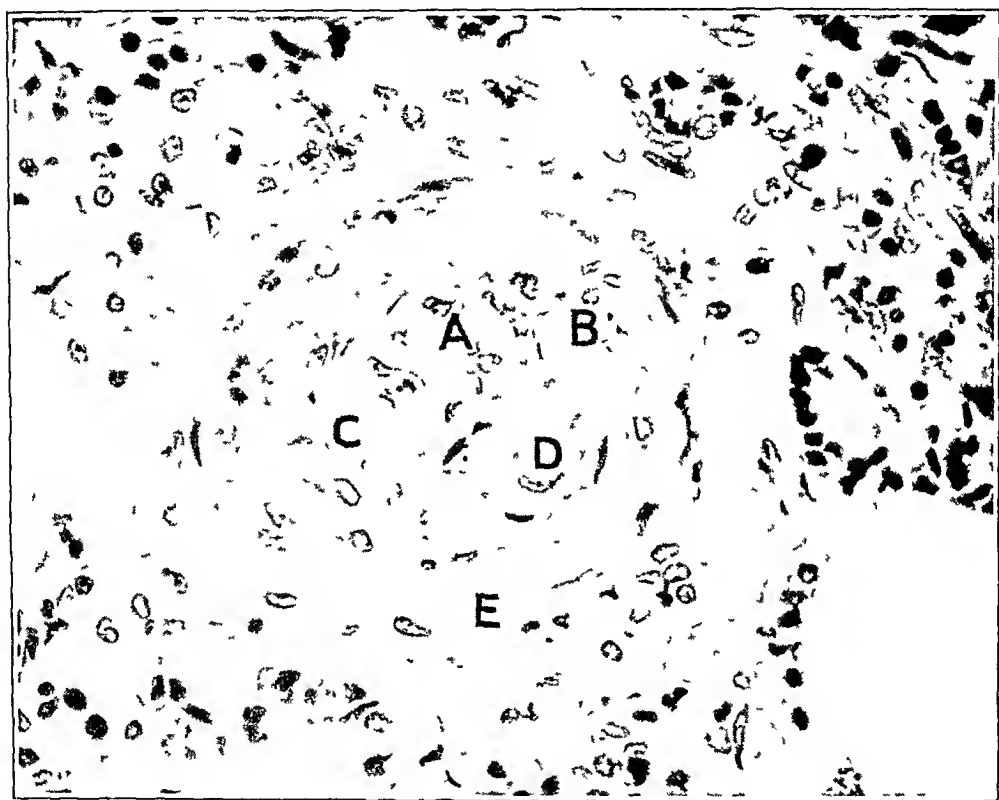


Fig 7—Vascular lesion of the lung (channeled vessel). Hematoxylin and eosin stain, high power. This section shows (A) proliferation of the endothelial cells with swelling and early granular degeneration, (B) intimal proliferation still showing swollen granular cells, (C) proliferated intima with replacement of the granular cells by scar tissue, (D) a canalized lumen and (E) the media.

*Postmortem Examination*—The diagnosis was chronic valvular disease (slight mitral stenosis), chronic polyserositis, nonbacterial thrombotic endocarditis of the mitral valves, meningo-encephalitis (nonsuppurative), diffuse endarteritis, infarcts of the spleen and kidneys, fatty degeneration of the liver, petechiae of the mesentery and omentum and follicular hyperplasia of the gastro-intestinal tract.

The body was that of an emaciated, pale young woman. Both pleural cavities were filled with firm adhesions. The pleural surfaces were everywhere roughened by adhesions, which were separated with difficulty. Adherent pericarditis was universal. The pleuropericardial space was obliterated by adhesions. On the

anterior cusp of the mitral valve was a continuous narrow ridge of confluent friable vegetations, a similar but discontinuous yellow ridge was present on the posterior cusp. Microscopically there was organizing pericarditis. There was a blood platelet thrombus on the mitral valve superimposed and combined with a superficial valvular substance showing eosinophilic change. There was low grade lymphocytic valvulitis of the mitral valve, some thickening of the cusp and a mild inflammatory lesion of the ring. However, there were no rheumatic auricular lesions and no Aschoff bodies, and the valvulitis was not that of active rheumatic infection. The appearance of the mitral valve was interpreted as that of non-bacterial thrombotic endocarditis on a somewhat thickened cusp which had undergone some previous inflammatory, possibly rheumatic alteration.

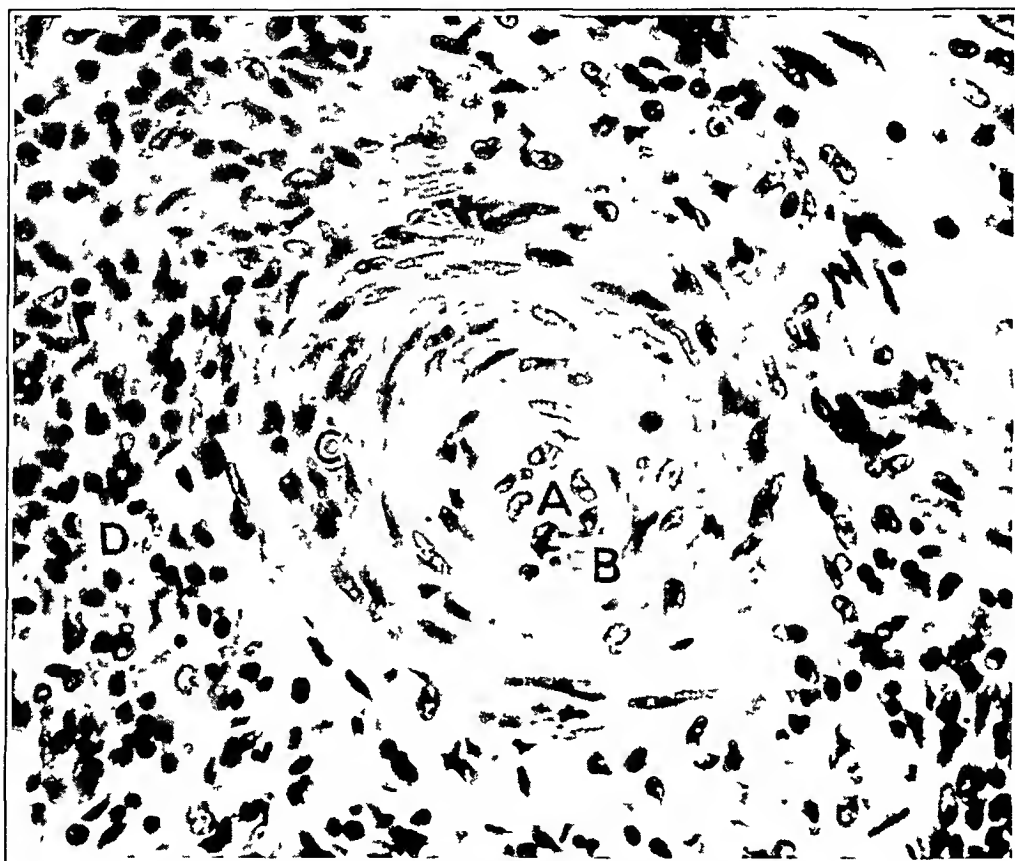


Fig 8—Vascular lesion of the lung. Hematoxylin and eosin stain, high power. This section shows (A) a markedly narrowed lumen lined by swollen endothelial cells, (B) a proliferated intima still showing swollen granular cells, (C) a hypertrophied and edematous media and (D) perivascular lymphocytic infiltration.

The pulmonary artery was considerably dilated. The peritoneal cavity contained a fairly large quantity of clear amber fluid. There were adhesions between the liver and the inferior surface of the diaphragm and between the spleen and the diaphragm. Loops of ileum and cecum were adherent to the uterus and the right ovary. The cecum and ascending colon were adherent to the lateral wall of the peritoneal cavity. The kidneys showed coarse granulation due to depressed scars of infarction. The glomerular epithelium showed enlargement and proliferation. Thickening and infiltration of the meninges were noted. There were con-

siderable vascular alterations throughout several organs. The capillaries and smaller arteries of the heart showed intimal thickening and in places partial or complete occlusion of the lumen. This appeared to be due to swelling and proliferation of endothelial cells with granular degeneration and fusion. In the process of organization these granular plugs formed marked intimal thickening or occlusion with canalization. Lymphocytic infiltration occurred around these vessels. Similar alterations were present in the vessels of the kidney, stomach, pancreas, brain and lung (figs 7 and 8).

*Comment*—The essential features in this case were the febrile illness lasting for almost a year with only a brief intermission, sterile blood cultures, polyarthritis, pleural and pericardial rubs with signs of pleural effusion, symptoms of nephritis, secondary anemia, abdominal symptoms resembling appendicitis and cerebral complications. With the discovery of symptoms of arthritis the patient was considered to be suffering from rheumatic fever. However, long-standing fever and evidences of nephritis suggested that this might be a case of subacute bacterial endocarditis with sterile blood cultures. Postmortem examination revealed, as in the previous cases, inflammation of the serous membranes lining the pleura, pericardium and peritoneum, a nonbacterial, nonrheumatic thrombotic endocarditis, diffuse endarteritis with plugging and canalization of vessels and subacute nonsuppurative encephalitis. The nonbacterial thrombotic endocarditis was superimposed on an old rheumatic valve, a relationship emphasized in our general description of this form of endocarditis.<sup>1</sup>

#### COMMENT

*Clinical Features*—Certain manifestations were present in all these cases. The patients were women, three of them being about 20 years of age and one 48. For the most part, the clinical course was that of a general infection, but numerous aerobic and anaerobic blood cultures were persistently sterile. The course of the disease was prolonged and progressive, and except for brief remission there was persistent fever during the entire period of the illness (in one case for three years).

The onset was usually marked by acute polyarthritis involving both the large joints and the small joints of the fingers and hands. A striking feature was the development in two of the four cases of marked joint deformities with a spindle-shaped appearance of the fingers, as in chronic infectious arthritis, tuberculosis or syphilis.

Early in the course of the disease a pericardial rub was heard in all four cases and a pleural rub in three cases. There were physical and roentgen signs of pleural effusions in all instances. Although rather large quantities of ascitic fluid were found in every case at postmortem examination, this was verified by aspiration only once during life.

There was never striking evidence of endocardial involvement. A systolic murmur was generally present. The electrocardiographic

changes were compatible with adhesive pericarditis. Marked secondary anemia was a prominent feature. Despite persistent fever, leukocytosis was never marked. Urinary abnormalities were frequent. Albumin and casts were regularly present, and leukocytes and erythrocytes were generally noted. There was evidence of renal impairment only in the third case. Death resulted from increasing toxemia, anemia and cachexia.

*Pathologic Condition*—Inflammatory changes were present not only in the pericardium, the pleurae and the peritoneum but also in the serous lining of the joint spaces in the two cases in which these were available for examination. There were marked pleural and pericardial adhesions, generally with obliteration of the respective cavities but occasionally with remnants of effusions. In the peritoneal cavity were noted a large amount of clear ascitic fluid, fine or firm adhesions binding the loops of intestine to each other or to the parietal peritoneum (without intestinal obstruction) and generally perihepatitis and perisplenitis with adhesions to neighboring structures. The synovial membranes of various joints, in the two cases in which these were available for examination, were thickened and edematous and showed marked endothelial hyperplasia and cellular inflammation, with occasional perivascular infiltrations.

In each case the heart showed nonbacterial thrombotic deposits on one or more of the valves of the type described in detail elsewhere.<sup>1</sup> These vegetations consisted of a conglomeration of blood platelet thrombi deposited on a valve which had undergone eosinophilic change, with little or no inflammatory reaction in the valve itself.

Vascular alterations were observed in every case. In the first case these were mild and consisted of occasional endarteritis and endophlebitis of the smallest vessels, particularly those of the myocardium. In the second case there was considerable thickening of the smallest arteries and arterioles of the lungs, myocardium, brain and thyroid gland, occasionally with marked narrowing of the lumens or complete obliteration by hyaline or granular plugs. Similar but more extensive changes were present in the fourth case, the vessels of the lung showing necrosis as well as inflammation. In case 3 there was marked necrotizing panarteritis involving the heart, kidneys, stomach and mesentery.

*Diagnosis*—The onset with polyarthritis frequently led to a diagnosis of acute rheumatic fever. However, there was neither constant nor definite evidence of valvular disease despite the prolonged course. There were no electrocardiographic changes suggesting rheumatic fever. The early development of ankylosis and of articular deformity, with the production of spindle-shaped joints, is absent or rare in rheumatic fever. At postmortem examination there was no evidence of recent rheumatic infection.

The condition frequently simulated a general infection. Subacute bacterial endocarditis was a diagnosis frequently entertained. However, blood cultures were persistently sterile, and embolic phenomena were absent. Tuberculosis was sometimes considered because of the pleuro-pulmonary signs, the articular phenomena and the continued fever. These same symptoms resembled those of atypical verrucous endocarditis (Libman and Sacks). At postmortem examination the flat, spreading variety of vegetation, the involvement of mural endocardium and the severe inflammatory and necrotizing lesions in the valves described by Libman and Sacks<sup>2</sup> and by Gross<sup>4</sup> were absent in our cases.

Recently Baehr, Klemperer and Schiffrin<sup>5</sup> described twenty-three cases of disseminated lupus erythematosus associated with extensive vascular lesions and frequently with endocarditis. Some of their patients showed features characteristic of the Libman-Sacks variety of endocarditis, while others revealed the nonbacterial thrombotic endocarditis noted in our cases. Baehr and his co-workers found that a high percentage of their patients had had arthritis and inflammation of the pleura and pericardium in addition to the vascular lesions and endocarditis. The absence of lupus erythematosus in our cases may not be an essential difference. It is conceivable that a condition belonging to the same general type as that described by Baehr and his co-workers might occur without the striking cutaneous lesions but with the other associated clinical and pathologic features of the disease. It should be added, however, that aside from the absence of lupus erythematosus in our cases, the articular manifestations were more marked and produced more conspicuous deformities than those that occurred only occasionally in the cases of Baehr and his co-workers, the involvement of the serous membranes was more extensive and dominated the clinical picture and the vascular lesions were not altogether identical. Two other cases similar to those here described and to those of Baehr, Klemperer and Schiffrin were reported by Tremaine<sup>6</sup> and Christian.<sup>7</sup>

*Etiology and Pathogenesis*—These cases appear to form a definite clinical syndrome of unknown etiology. The salient characteristic of the disease was its tendency to affect serous membranes (pleurae, pericardium, peritoneum and synovial membranes throughout the body) and the endothelial lining of the blood vessels and of the heart (endocardium). Certain clinical and pathologic features suggested an infec-

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4 Gross, Louis, in Contributions to the Medical Sciences in Honor of Dr Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol 2, pp 527-550

5 Baehr, G, Klemperer, P, and Schiffrin, A. Tr. A. Am. Physicians **50** 139-155, 1935

6 Tremaine, M. J. New England J. Med. **211** 754-759, 1934

7 Christian, H. A. M. Clin. North America **18** 1023-1026, 1935

tious process. The vascular lesions differed in many respects from those described by Wiesel,<sup>8</sup> Wiesner,<sup>9</sup> Siegmund<sup>10</sup> and others in a number of infectious diseases but resembled some of those observed in rheumatic fever (Gross<sup>11</sup>). In addition, extensive vascular lesions of the necrotizing variety, such as those present in one of our cases, have been described in association with rheumatic fever.<sup>12</sup>

The relationship of our cases to those of Libman and Sacks,<sup>2</sup> Baehr, Klemperer and Schiffin,<sup>5</sup> Tiemane<sup>6</sup> and Christian<sup>7</sup> must await the discovery of the specific etiology or the determination of definite rigid criteria for the clinicopathologic syndrome. Although the possibility that these are atypical cases of rheumatic fever cannot be entirely excluded, studies recently completed<sup>1</sup> indicate that they probably all comprise a definite clinical-pathologic syndrome. For the present it is important to draw attention to this group of cases so that the condition may be recognized clinically and may be studied for further elucidation.

#### SUMMARY

In a previous study on indeterminate forms of endocarditis cases of nonbacterial thrombotic endocarditis were described and classified. Certain groups appeared to possess clinical and pathologic features in common.

This report deals with one of these groups, comprising four cases, in which the disease was characterized by prolonged fever, polyarthritis, inflammation of serous membranes (pleura, pericardium, peritoneum, endocardium and synovial membrane) and a variety of vascular lesions.

The clinical course was that of a general infection, but cultures of the blood were sterile. The onset was marked by inflammatory polyarthritis involving the large and small joints. Ankylosis and deformities developed in two of the four cases. There were pleural and pericardial effusions. Symptoms of endocardial involvement were indefinite. Symptoms of renal and cerebral involvement were frequent. The differential diagnosis lay between a general infection, subacute bacterial endocarditis, rheumatic fever and tuberculosis.

8 Wiesel, J. *Wien klin Wchnschr* **19** 723-725, 1906.

9 Wiesner, R. *Wien klin Wchnschr* **19** 725-726, 1906.

10 Siegmund, H. *Zentralbl f allg Path* **35** 276-277, 1924.

11 Gross, Louis, Kugel, M. A., and Epstein, E. Z. *Am J Path* **11** 253-279, 1935.

12 Friedberg, C. K., and Gross, Louis. *Periarteritis Nodosa (Necrotizing Arteritis) Associated with Rheumatic Heart Disease, with a Note on Abdominal Rheumatism*, *Arch Int Med* **54** 170-198 (Aug) 1934.

13 Friedberg, C. K., and Gross, Louis. *The Cardiac Lesions in the Libman-Sacks Syndrome, with a Consideration of Its Relationship to Acute Diffuse Lupus Erythematosus*, to be published.



At necropsy there were adhesive pleuropneumonitis with obliteration of the pleural and pericardial cavities, an excessive quantity of fluid in the peritoneum, perihepatitis, and perisplenitis with adhesions between the liver and the diaphragm, between the spleen and the diaphragm, between the intestines and between the parietal and the visceral peritoneum. The synovial membranes, in the two cases in which these were available for examination were thickened and edematous and showed marked endothelial hyperplasia and cellular inflammation with occasional perivascular infiltrations. The heart showed nonbacterial thrombotic deposits on one or more of the valves. There was no evidence that these were of rheumatic origin. There were a variety of vascular lesions in many organs, including endothelial proliferation, endothelial desquamation with granular degeneration and swelling, narrowing or obstruction of the lumen by plugs, intimal proliferation and actual necrosis of the vessel wall.

The clinical and pathologic features suggested that we were dealing with some infectious agent with a pronounced toxic effect on structures lined by endothelium.

# PATHOLOGY AND PHARMACOLOGY OF CARDIAC SYNCOPE AND SUDDEN DEATH

M H NATHANSON, M D

LOS ANGELES

Cardiac syncope is sudden loss of consciousness due to cerebral anemia of cardiac origin. Sudden "cardiac death" may be considered as fatal cardiac syncope.

## PATHOLOGY OF CARDIAC SYNCOPE AND SUDDEN DEATH

Temporary loss of consciousness in cardiac disease is usually associated with complete heart block, i e., the Adams-Stokes syndrome. Careful histologic examination of the myocardium is frequently required to discover the myocardial lesion, which consists in most instances of fibrosis affecting the junctional tissues. The remainder of the myocardium usually shows only minimal changes.

Sudden death is a prominent feature of disease of the coronary arteries. In a previous analysis<sup>1</sup> of 113 autopsies at which occlusive coronary disease was noted, the clinical picture was congestive heart failure in approximately 40 per cent and sudden death without congestive heart failure in 60 per cent. In most of the cases of the latter group the clinical syndrome of angina pectoris was presented. There are two essential features of angina pectoris: (1) attacks of pain, usually in the chest, and (2) a tendency to sudden, unexpected death. The literature contains considerable material on the nature, prevention and treatment of the attack but little on the mechanism and therapy of the other important feature, the sudden death.

An analysis was made of 142 autopsies showing occlusive coronary disease in which sudden death occurred. The purpose of this study was to determine the frequency of structural changes in the myocardium sufficient to explain the sudden death. Cases were excluded in which there was a history of congestive heart failure and in which there was evidence of passive congestion of the liver at autopsy. Cases were also excluded in which there was a history of acute dyspnea or pain, with death deferred for a variable period, and in which edema of the lungs was present at autopsy. This series consisted essentially of cases in

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<sup>1</sup> Nathanson, M H. Disease of the Coronary Arteries, *Am J M Sc* **170**, 240, 1925.

which sudden death occurred at a time when the circulation was competent. The study is summarized in the tables 1 to 3.

Table 1 shows the age distribution by decades. The youngest patient was 26, and the oldest, 83, the average age at the time of death being 58.1 years.

Table 2 shows the weights of the hearts as recorded in 139 autopsies. Marked cardiac hypertrophy (600 Gm. or more) was exceptional, occur-

TABLE 1—*Age Distribution of One Hundred and Forty-One Patients with Coronary Disease Terminated by Sudden Death*

Age, Years	Number of Cases	Percentage
20 to 30	1	0.7
30 to 40	5	3.6
40 to 50	24	17.0
50 to 60	40	28.3
60 to 70	53	37.5
70 to 80	16	11.3
80 to 90	2	1.4

TABLE 2—*Weights of Hearts of One Hundred and Thirty-Nine Patients with Coronary Disease Terminated by Sudden Death*

Weight of Heart, Gm.	Number of Cases
200 to 299	2
300 to 399	55
400 to 499	47
500 to 599	31
600 to 699	4

The heart weighed less than 450 Gm. in 93 cases and more than 450 Gm. in 40 cases.

TABLE 3—*Gross Structure of the Myocardium in Patients with Coronary Disease Terminated by Sudden Death*

	Number of Cases	Percentage
Normal	70	50
Fibrosis	31	22
Myomalacia cordis	30	21
Rupture of heart	11	7
Total	142	

ing in only 4 instances. In approximately two thirds of the cases the cardiac weight was less than 450 Gm. This analysis indicates that sudden death in cases of coronary disease is usually associated with a heart either normal in size or only moderately hypertrophied.

Table 3 gives an analysis of the gross structure of the myocardium in 142 cases. According to the gross appearance of the myocardium the cases were arbitrarily divided into four groups. In the group in which the myocardium is recorded as normal it was practically normal on section or showed only streaks of fibrosis. In the group in which

fibrosis was present, there was either extensive diffuse fibrosis or large localized patches of scarring. The remaining two groups consisted of cases in which the heart showed one or more recent infarcts or areas of softening and in which rupture of the heart had occurred.

It is apparent that only acute and extensive myocardial damage can account for the sudden change from a competent circulation to complete cessation of the circulation and death. Fibrosis of the myocardium may affect the efficiency of the heart to only a slight degree. It is well known that a large infarction frequently heals, permitting normal cardiac activity for a period of years, a large scar of the healed infarct being present at autopsy. Rupture of the heart, the only myocardial change which can definitely account for sudden death, was present in only 7 per cent of the cases at autopsy, indicating that a structural basis for sudden death is infrequent.

Table 4 shows the incidence of coronary thrombosis in 142 autopsies and its frequency in the four subgroups. Thrombosis of the large

TABLE 4—*Incidence of Coronary Thrombosis in Patients with Coronary Disease Terminated by Sudden Death*

Gross Structure of Myocardium	Number of Cases	Cases of Coronary Thrombosis	Percentage
Normal	70	12	17.0
Fibrosis	31	6	20.0
Myomalacia cordis	30	15	50.0
Rupture of heart	11	6	54.0
Total	142	39	27.5

coronary branch occurred in 39 cases, or 27.5 per cent. As might be expected, the incidence was higher in the groups in which there was a more acute and severe degree of myocardial damage.

*Comment*—Necropsy observations in cases of coronary disease failed to explain the sudden death in most instances. The heart was usually of normal size or only moderately enlarged. The structure of the myocardium in all cases, with the exception of a small group, was compatible with life and the continuance of a fairly efficient circulation. In most cases there was no evidence of acute obstruction of a large coronary branch. The necropsy evidence therefore indicates that the mechanism of sudden death in coronary disease is usually physiologic. It is to be emphasized that there are only two physiologic mechanisms within the heart which can account for a sudden cessation of the circulation leading either to temporary syncope or to death, namely, a cardiac or ventricular standstill and ventricular fibrillation.

#### PHARMACOLOGY OF CARDIAC SYNCOPE AND SUDDEN DEATH

The action of drugs on cardiac standstill and ventricular fibrillation was studied by pharmacologic methods which are applicable to man.

It is well known that ventricular standstill is the usual mechanism underlying the transient syncopal attacks of heart block. Although Allbutt<sup>2</sup> stated the belief that a vagus standstill of the entire heart is the cause of death in angina pectoris, the preponderance of evidence indicates that fatal cardiac syncope is usually due to ventricular fibrillation.

*Cardiac Standstill*—In cases of complete heart block the ventricles, deprived of the influence of the sinus node, beat independently. The continuance of ventricular contraction is dependent on the rhythmic power of the ventricles. Being but poorly equipped with the property of rhythmicity, the ventricles at times fail to produce the necessary stimulus, and ventricular standstill and syncope follow. The therapeutic indication is the administration of drugs which will increase the rhythmic property of the ventricles. In previous reports<sup>3</sup> it was demonstrated

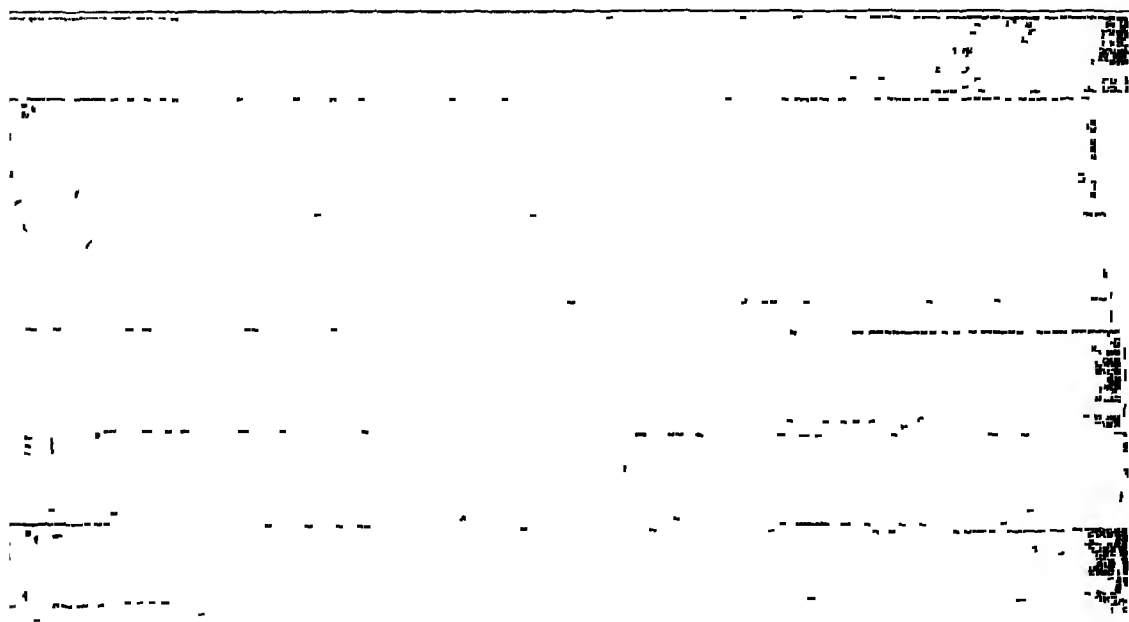


Fig 1 (H B)—A shows a standstill of seven and six-tenths seconds induced by pressure on the right carotid sinus (arrow). B was taken one minute after the intravenous injection of 0.05 mg of epinephrine and shows the standstill abolished by the development of ventricular rhythm. The lowest strip shows the disappearance of the effect after fifteen minutes.

that the cardiac standstill which can be induced in many human subjects by pressure on the right carotid sinus may be utilized for the study of the action of drugs on cardiac rhythmicity. The pressure on the carotid sinus in these cases eliminates the activity of the sinus node.

2 Allbutt, Clifford. *Diseases of the Arteries Including Angina Pectoris*, London, Macmillan & Company, 1915, vol 2.

3 Nathanson, M. H. Effect of Drugs on Cardiac Standstill Induced by Pressure on the Carotid Sinus, *Arch Int Med* **51** 387 (March) 1933. Further Observations on the Effect of Drugs on Induced Cardiac Standstill, *ibid* **54** 111 (July) 1934.

Cardiac standstill follows since no other portion of the heart possesses the rhythmic function to a sufficient degree for the development of a new pace-making center. It was demonstrated that after the administration of certain drugs cardiac standstill was not influenced, indicating that these substances were without effect on cardiac rhythmicity. Ineffective compounds were digitalis, caffeine, pyridine beta-carbolic acid di-ethylamine, metiazol, thyroxine and calcium gluconate. It was found, however, in 10 subjects that epinephrine (fig 1), by initiating a new rhythmic center in the ventricles, exerts a powerful effect in the prevention of induced cardiac standstill. It was demonstrated that ephedrine (fig 2) and other compounds related in structure to epinephrine also

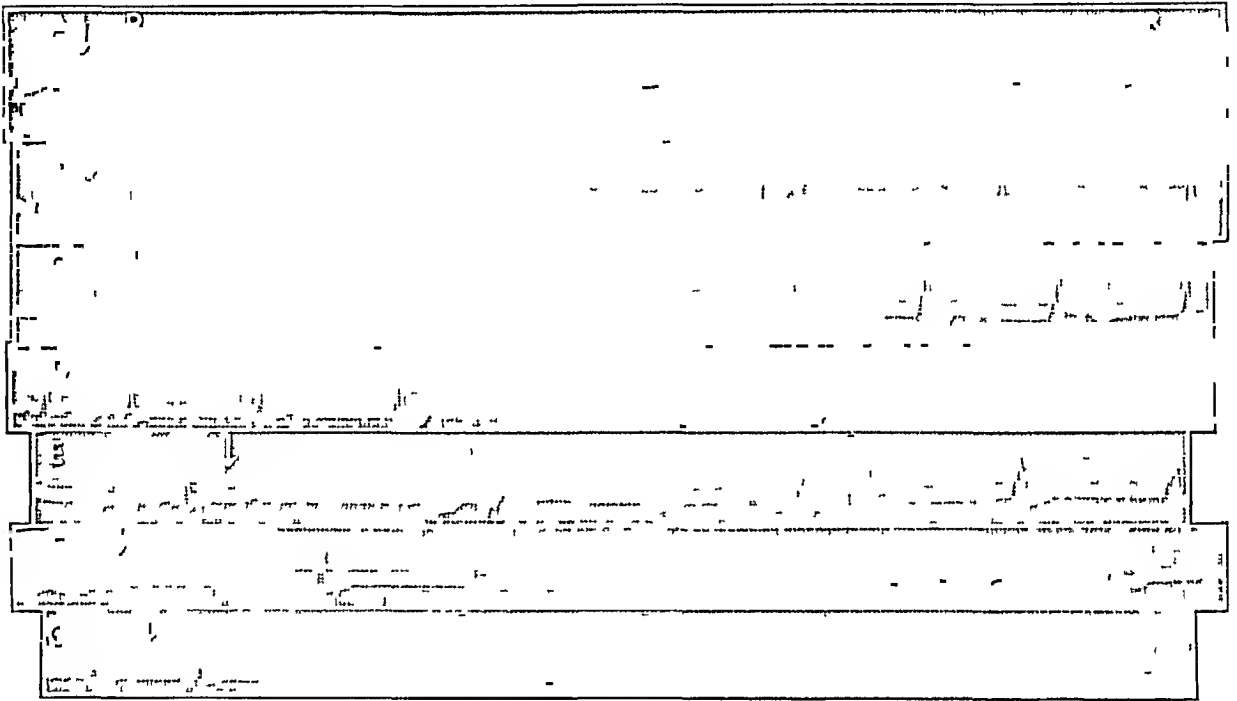


Fig 2 (H B) —A shows an induced standstill of nine and six-tenths seconds. The lower strips were taken after 100 mg of ephedrine sulfate had been injected intravenously. The standstill was abolished by the development of ventricular rhythm. The rate of the new pacemaker is similar to that following the administration of 0.05 mg of epinephrine (fig 1). This indicates that the ratio of the activity of ephedrine to that of epinephrine is 1 to 2,000.

had a definite action in increasing ventricular rhythmicity. It was possible to carry out a quantitative study of these compounds, and the intensity of the effect increased as these substances approached the composition of epinephrine itself. The effectiveness of the drugs of the epinephrine series indicates that the response of the heart is the result of a specific pharmacologic action, stimulation of the cardiac-accelerator mechanism, and only drugs possessing this action are likely to be effective in cardiac standstill.

*Ventricular Fibrillation*—The preponderance of evidence indicates that while cardiac standstill is the basis for temporary cardiac syncope, ventricular fibrillation is the mechanism underlying the fatal syncope of coronary disease. The evidence may be summarized as follows:

1 Hering<sup>4</sup> has stated that in twenty years of experimental work on animals he has frequently observed standstill of the entire heart produced by stimulation of the vagus nerve. This is characterized by being of relatively short duration with a spontaneous return of activity. There is temporary circulatory insufficiency but not death. He said that he knew of no experiment in which the whole heart or the ventricles have been brought to a permanent standstill. Either the sinus node regains its activity or another focus acts.

2 In contrast to standstill, ventricular fibrillation in the experimental animal is usually a lethal arrhythmia, persisting until death. There is usually no return of a coordinated contraction. The collapse in cases of angina pectoris is just such an irreversible condition. In cases of heart block, on the other hand, the rule is repeated attacks with recovery.

3 Perhaps the most striking evidence correlating ventricular fibrillation and coronary disease is the high incidence of ventricular fibrillation following experimental ligation of the coronary arteries.

4 Extrasystoles and ventricular tachycardia, which may be considered as prefibrillation arrhythmias, are frequently observed associated with clinical evidence of acute coronary closure.

Although temporary cardiac standstill can be induced easily and with safety in human subjects, it is obvious that ventricular fibrillation may not be investigated in the same manner. The exact nature of ventricular fibrillation is not clear. There is considerable evidence, however, that cardio-accelerator nerve impulses and epinephrine play an important part in the genesis of this arrhythmia. Observations on experimentally induced ventricular fibrillation strongly indicate that epinephrine acts synergistically with some other factor to increase ventricular rhythmicity leading to ventricular fibrillation. Levy and Lewis<sup>5</sup> produced ventricular fibrillation in cats under light chloroform anesthesia by the injection of epinephrine.

Rothberger and Winterberg<sup>6</sup> found in dogs that stimulation of the accelerator nerves or the introduction of epinephrine induced ventricular

4 Hering, H. E. *Der Sekundenherztod mit besonderer Berücksichtigung des Herzkammerflimmerns*, Berlin, Julius Springer, 1917.

5 Levy, A. J., and Lewis, T. Heart Irregularities Resulting from the Inhalation of Low Percentages of Chloroform Vapour, and Their Relationship to Ventricular Fibrillation, *Heart* 3: 99, 1912.

6 Rothberger, C. J., and Winterberg, H. Ueber die experimentelle Erzeugung extrasystolischer ventrikulärer Tachykardie durch Acceleransreizung, *Arch f. d. ges. Physiol.* 142: 461, 1911.

fibrillation in a heart partially poisoned with barium chloride Otto<sup>7</sup> consistently produced ventricular fibrillation in dogs by ligation of branches of the coronary circulation When the same procedure was carried out subsequent to section of the sympathetic fibers, ventricular fibrillation did not follow Nahum and Hoff<sup>8</sup> found that inhalation of benzene regularly produced ventricular fibrillation and this did not occur in animals after adrenalectomy More recently Hoff and Nahum<sup>9</sup> showed that removal of the stellate ganglions and adrenal glands enormously decreased the susceptibility of the ventricles to fibrillation following electric shock These observations indicate that epinephrine is an important exciting agent in the development of fibrillation in a ventricular myocardium sensitized by various methods, such as poisoning with chloroform, barium chloride and benzene, reduction of the blood supply or application of electric stimuli It appears, therefore, that the tendency to ventricular fibrillation should be lessened by the application of drugs which counteract the effect of epinephrine on the ventricles

In the present clinical study epinephrine was introduced in doses sufficient to increase ventricular rhythmicity to the point of the development of an ectopic ventricular rhythm The action of various drugs in the prevention of this rhythm was then observed There is a relationship between these induced ventricular rhythms and ventricular fibrillation Ventricular fibrillation in its fully developed form does not come on abruptly First, the cardiac rhythm is disturbed by premature contractions of ventricular origin which increase in number until groups are formed Other foci of activity are usually added The heart then accelerates in response to these new impulses and is eventually controlled by them exclusively A stage of rapid ventricular tachycardia originating from either a single focus or several ventricular foci frequently appears before the full development of the fibrillation In the present study it was found that these types of ventricular rhythm could be induced in many human subjects by the intravenous injection of epinephrine The induced ventricular rhythm represents a physiologic state in the ventricles similar to but of a lesser degree than that which exists in fibrillation It is therefore evident that the action of drugs on the induced rhythm may be applicable to ventricular fibrillation

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7 Otto, H L Untersuchungen uber die Nn accelerantes cordis, *Arch f d ges Physiol* **217** 147, 1927

8 Nahum, L H, and Hoff, H E The Experimental Production of Ventricular Fibrillation and Its Prevention by B-Methyl Acetylcholine Chloride, *Am J Physiol* **109** 78, 1934

9 Hoff, H E, and Nahum, L H The Nature of Ventricular Fibrillation Following Electric Shock and Its Prevention by Acetyl-B-Methylcholine Chloride *Am J Physiol* **110** 675, 1935



## EXPERIMENTS

The experiments were carried out in the following manner. Elderly persons were selected, and a control electrocardiogram was made in each case. Epinephrine hydrochloride, 0.1 mg., was then injected intravenously, and a continuous electrocardiogram was made for five minutes. In most cases frequent extrasystoles from multiple ventricular foci developed within one minute, with a return to the normal rhythm usually within four minutes following the injection. The drug to be studied was then administered, after a suitable period 0.1 mg. of epinephrine was again administered intravenously, and the reaction was observed in the electrocardiogram.

*Quinidine*—This drug was used because of its well known action in the restoration of the normal rhythm in cases of auricular fibrillation and in the prevention of a return of the fibrillation. Quinidine acts also on ventricular muscle. Scott<sup>10</sup> and Levine and Fulton<sup>11</sup> found that quinidine was effective in the prevention and treatment of ventricular tachycardia. Dock<sup>12</sup> reported a case in which maintenance doses of quinidine prevented attacks of ventricular fibrillation. H. D. Levine<sup>13</sup> demonstrated that experimental ventricular fibrillation was inhibited by quinidine. Jackson, Friedlander and Lawrence<sup>14</sup> showed that quinidine tends to counteract the development of ventricular fibrillation after the administration of digitoxin and aconitine.

In 10 cases 0.1 mg. of epinephrine hydrochloride injected intravenously induced rapid extrasystolic arrhythmia from multiple ventricular foci. Quinidine sulfate was then administered orally in increasing doses for five or six days. On the last day of the experiment the amount usually administered was 2 or 2.2 Gm. in divided doses. In 2 cases the maximum amount administered was from 0.8 to 1 Gm. One hour after the last dose of quinidine was administered 0.1 mg. of epinephrine hydrochloride was injected intravenously. In 8 cases the ventricular extrasystoles were entirely eliminated, and the reaction was merely sinus tachycardia. In the 2 instances in which the smaller doses were administered an occasional extrasystole from a single ventricular focus developed (figs. 3 to 10). These observations indicate that quinidine

10 Scott, R. W. Observations on a Case of Ventricular Tachycardia with Retrograde Conduction, *Heart* 9 297, 1921.

11 Levine, S. A., and Fulton, M. N. The Effect of Quinidine Sulphate on Ventricular Tachycardia, *J. A. M. A.* 92 1163 (April 6) 1929.

12 Dock, W. Transitory Ventricular Fibrillation as a Cause of Syncope and Its Prevention by Quinidine Sulphate, *Am. Heart J.* 4 709, 1929.

13 Levine, H. D. Effect of Quinidine Sulphate in Inhibiting Ventricular Fibrillation, *Arch. Int. Med.* 49 808 (May) 1932.

14 Jackson, D. E., Friedlander, A., and Lawrence, J. V. Experimental Investigation of Pharmacological Action of Quinidine, *J. Lab. & Clin. Med.* 7 311, 1922.

exerts a powerful action in the prevention of ventricular rhythm of a prefibrillation type

*Ergotamine*—It is well known that this drug paralyzes the ends of the sympathetic nerves and in the experimental animal counteracts and even reverses the pressor action of epinephrine. The doses required, however, are much larger than those which can be administered to human beings. Otto<sup>7</sup> has further demonstrated that even larger doses are necessary to paralyze the cardiac sympathetic innervation. In three cases ventricular rhythm of a prefibrillation type was induced by the intravenous injection of 0.1 mg of epinephrine hydrochloride. Ergotamine tartrate was administered in 1 mg doses in 1 instance intravenously and in 2 instances subcutaneously. After various intervals

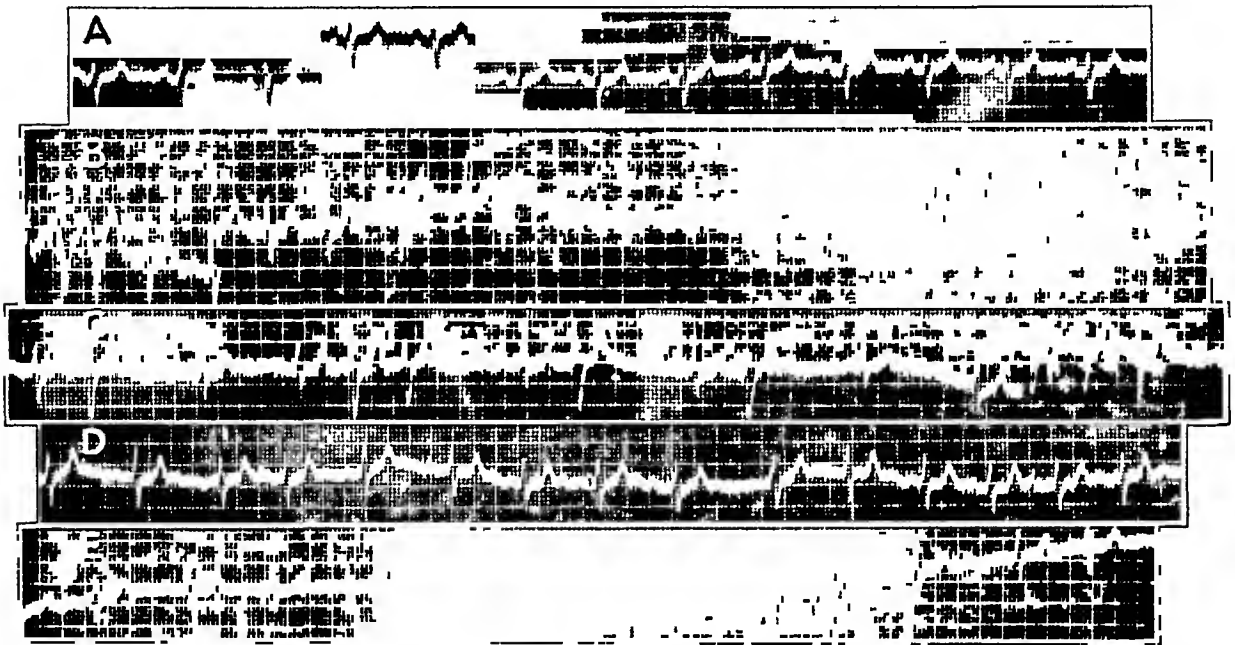


Fig 3 (J-Q)—Lead II. A was made before the injection of epinephrine, B, C, D and E were made one, two, three and four minutes, respectively, after the intravenous injection of 0.1 mg of epinephrine. B and C consist almost entirely of ectopic beats from multiple ventricular foci (a prefibrillation rhythm).

epinephrine was again injected intravenously. The reactions were similar to those produced prior to the administration of ergotamine, indicating that ergotamine in doses suitable for man is ineffective in preventing a prefibrillation rhythm.

*Potassium Salts*—There is experimental evidence that an excess of potassium ions in perfusion fluid prevents the formation of ectopic beats. Wiggers<sup>15</sup> and Hooker<sup>16</sup> found that potassium chloride is effective

15 Wiggers, C. J. Studies on Ventricular Fibrillation Caused by Electric Shock, *Am Heart J* 5:346, 1930.

16 Hooker, D. R. On the Recovery of the Heart in Electric Shock, *J Physiol* 91:305, 1929.

tive in the prevention of the ventricular fibrillation produced by electric shock Sampson and Anderson<sup>17</sup> have reported favorable results in the prevention of ventricular rhythm by the oral administration of potassium salts In 2 cases in which epinephrine injected intravenously produced

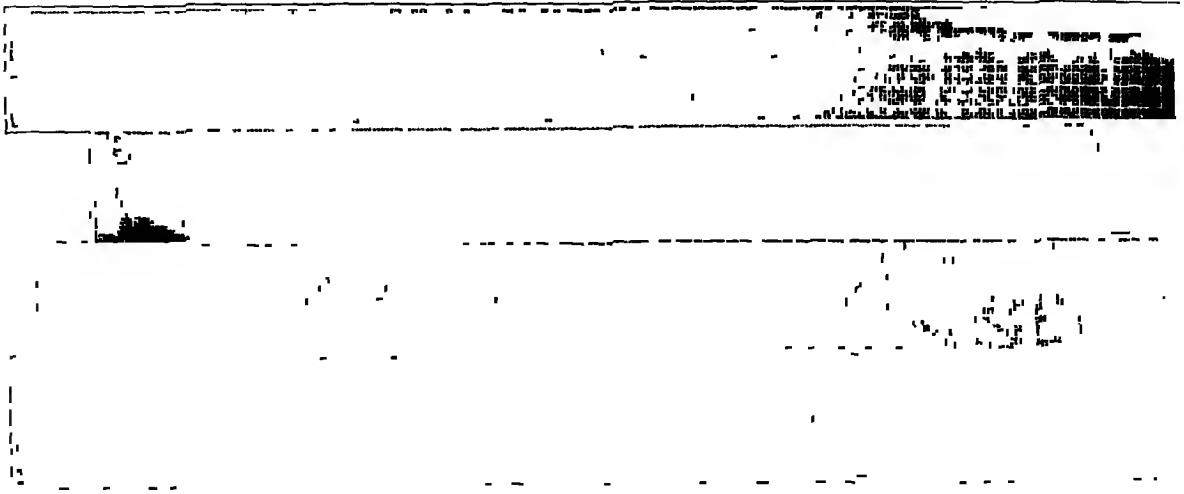


Fig 4 (J Q) —Lead II, one hour after the administration of 2 Gm of quimidine sulfate in divided doses *A* was made before the intravenous injection of epinephrine was given, *B*, *C* and *D* were made one, two and four minutes, respectively, after the injection of 0.1 mg of epinephrine The ectopic ventricular beats are entirely eliminated

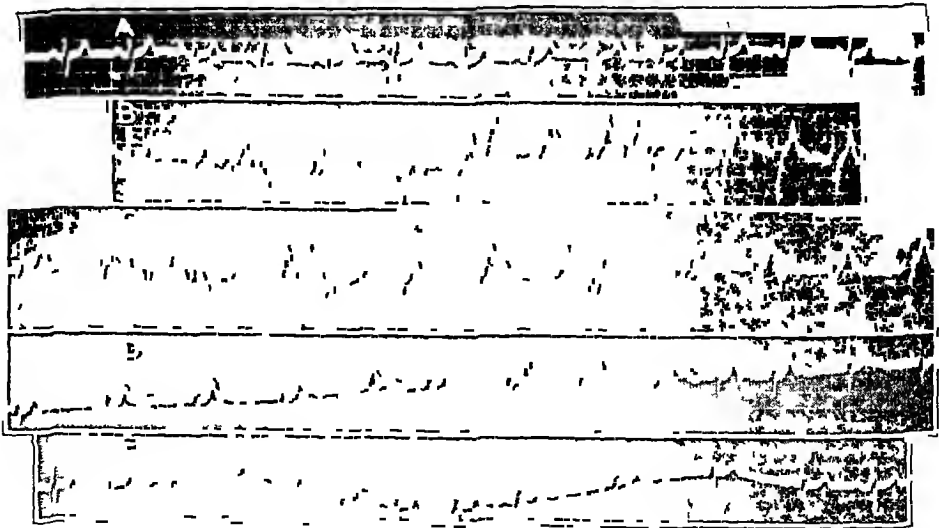


Fig 5 (J Q) —Lead II, six days after the use of quimidine was discontinued *A* was taken before epinephrine was given, *B*, *C*, *D* and *E* were taken one, two three and four minutes, respectively, after 0.1 mg of epinephrine hydrochloride was given Ectopic ventricular beats from multiple foci are again induced

17 Sampson, J J, and Anderson, E M The Treatment of Certain Cardiac Arrhythmias with Potassium Salts, *J A M A* 99 2257 (Dec 31) 1932

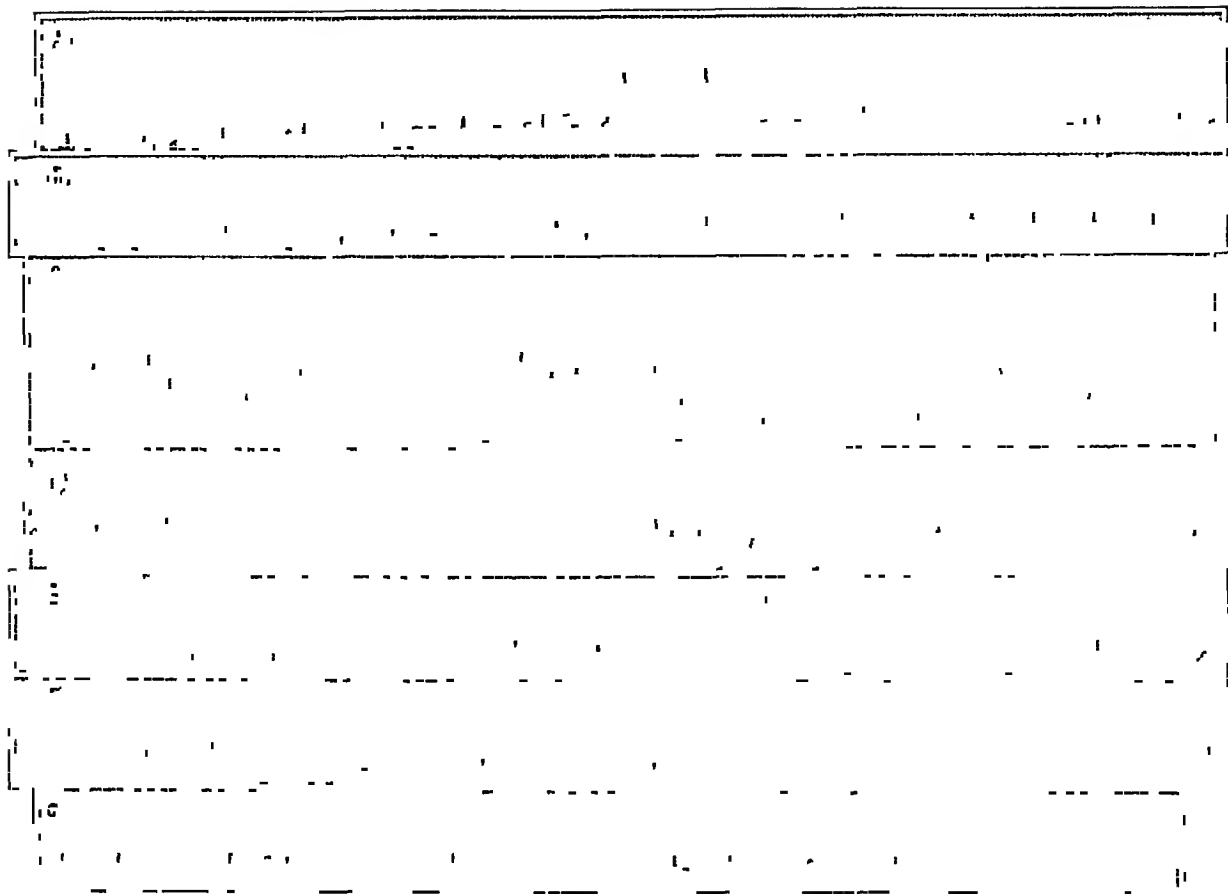


Fig 6 (M S) —Lead II *A* was taken before epinephrine was given, *B* was taken thirty seconds and *C*, *D*, *E*, *F* and *G* were taken at one minute intervals following the intravenous injection of 0.1 mg of epinephrine hydrochloride. Note that all beats in strip *C* and many in *D* are ectopic ventricular in origin.

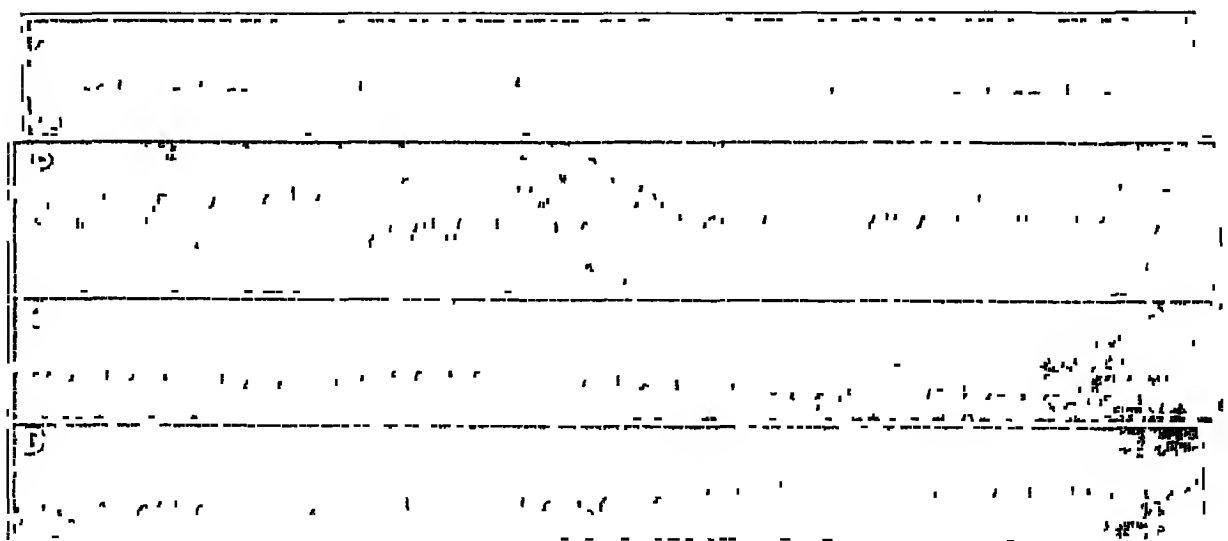


Fig 7 (M S) —Lead II, one hour after the administration of 1 Gm of quinidine sulfate. *A* was taken before epinephrine was given, *B*, *C* and *D* were taken one, three and five minutes, respectively, after the intravenous injection of 0.1 mg of epinephrine hydrochloride. Note the modification of the reaction as compared with that shown in figure 6. Only three ectopic ventricular beats were induced over a period of five minutes.

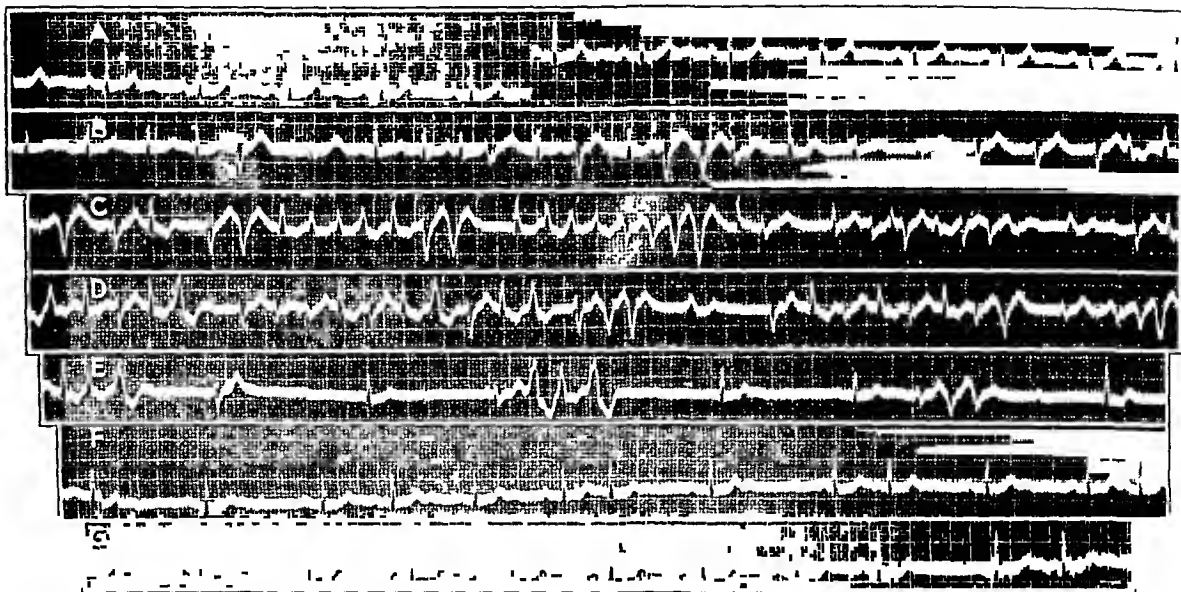


Fig 8 (G S)—Lead II *A* was taken before epinephrine was given. The lower strips were taken at one minute intervals following the intravenous injection of 0.1 mg of epinephrine hydrochloride. The epinephrine induced ectopic ventricular beats from multiple foci at a rapid rate and in groups. This is most marked in *C* and *D*.

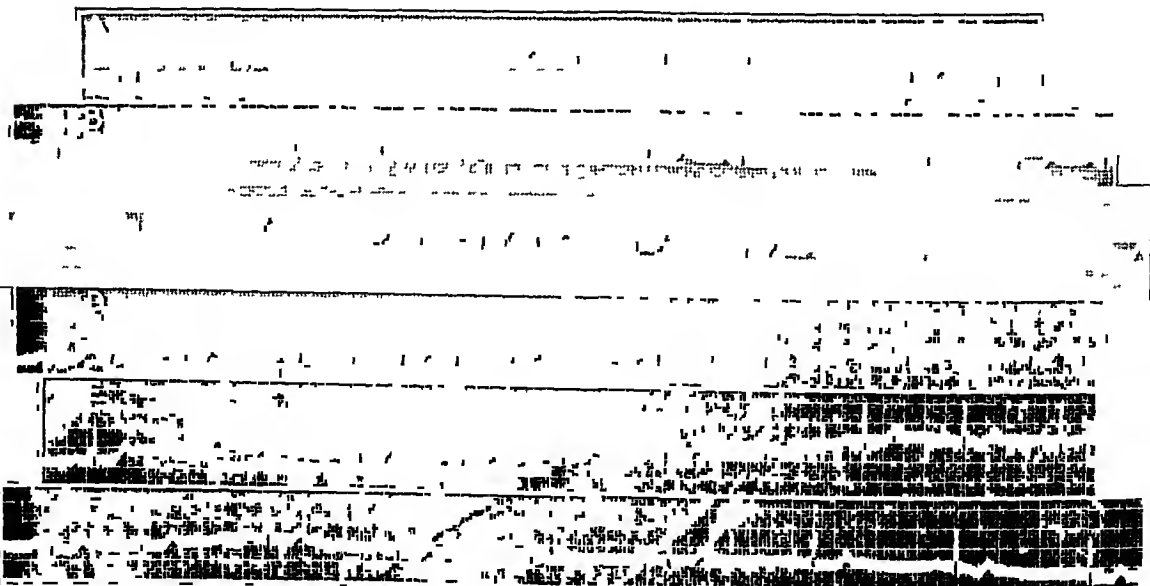


Fig 9 (G S)—Lead II, one hour after the administration of 2 Gm of quinine sulfate in divided doses. *A* was taken before epinephrine was given, *B*, *C*, *D*, *E* and *F* were taken at one minute intervals following the intravenous administration of 0.1 mg of epinephrine hydrochloride. Only one ectopic ventricular beat was induced (strip *C*). This reaction should be compared with that shown in figure 8.

a prefibrillation rhythm, potassium acetate was administered orally in daily doses of 6 and 8 Gm for four and five days, respectively. After this period the intravenous injection of epinephrine was repeated, and the reactions were similar to those induced prior to the administration of potassium acetate. These studies are insufficient to establish definitely the status of potassium salts. Larger doses may be necessary, since Sampson and Anderson found that some patients reacted only to large doses—up to 16 Gm.

*Acetyl-Beta-Methylcholine*—The administration of this substance produces the effects of stimulation of the vagus nerve, which theoretically may counteract the action of sympathetic stimulation on the ventricles. Nahum and Hoft<sup>8</sup> reported that ventricular fibrillation in cases of acute benzene poisoning can be prevented by the administration of

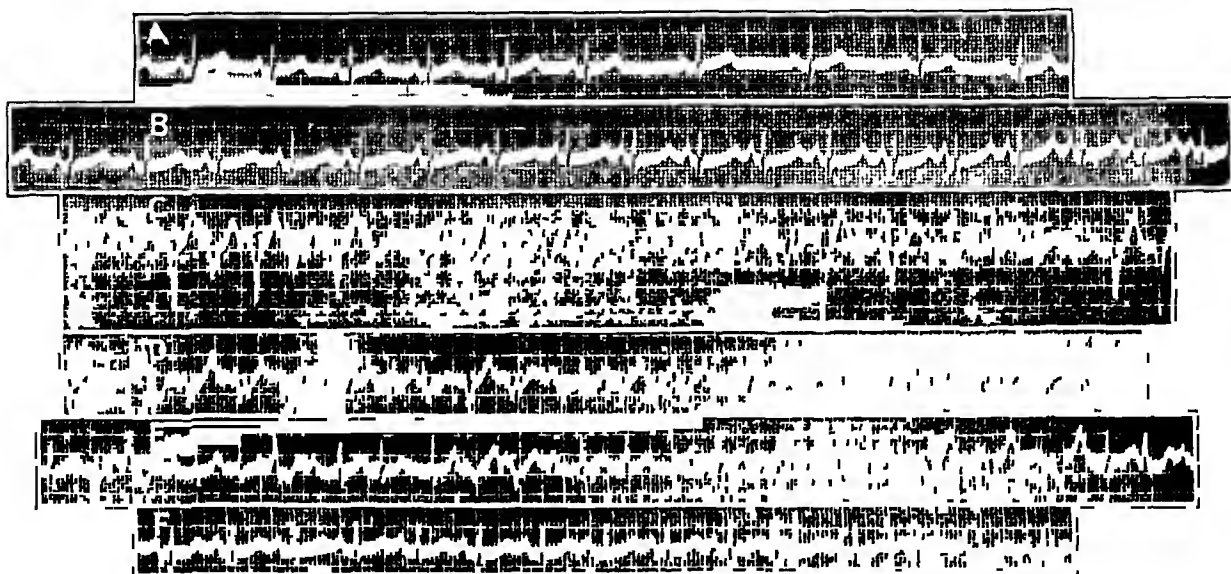


Fig 10 (M D)—Lead II, *A*, before the injection of epinephrine. *B* was taken thirty seconds afterward. The lower strips were taken at one minute intervals following the injection. Note the ectopic ventricular beats from multiple foci in strips *C*, *D* and *E*.

acetyl-beta-methylcholine. In the present study the reaction to 0.1 mg of epinephrine was observed before and after a subcutaneous injection of acetyl-beta-methylcholine chloride. The second dose of epinephrine was administered five minutes after the injection of 20 mg of acetyl-beta-methylcholine chloride. In 5 of 6 cases the ventricular rhythm induced by epinephrine was almost completely eliminated (figs 11 and 12). In 1 instance the effect of epinephrine was not modified to any degree.

*Sodium Amytal*—Seevers and Meek<sup>18</sup> produced ventricular rhythm in dogs by the intravenous injection of ephedrine. It was found that the

18 Seevers, M. H., and Meek, W. J. Barbiturate Protection from Cardiac Irregularities Induced by Ephedrine, *J. Pharmacol. & Exper. Therap.* **48**: 286, 1933.

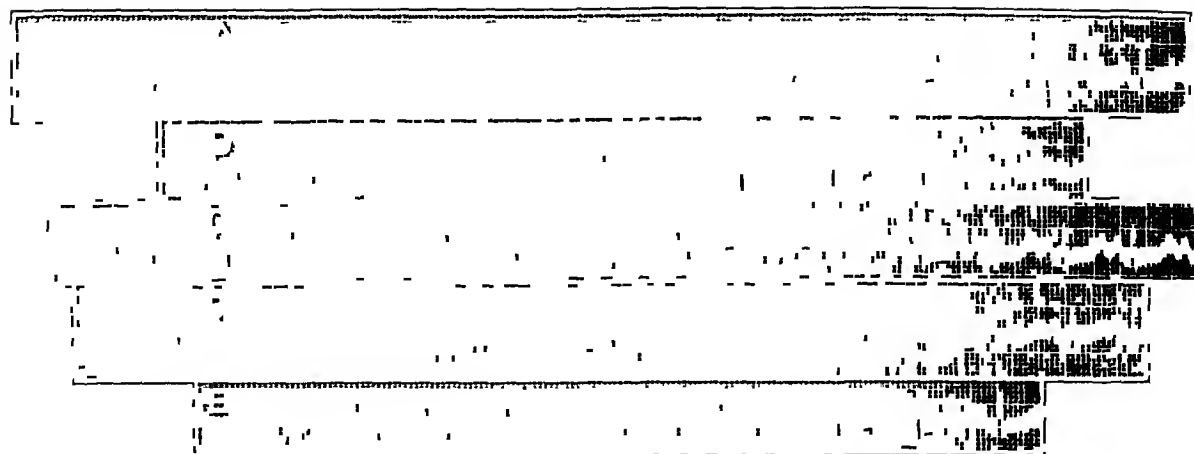


Fig 11 (M D) —Lead II, *A*, before the administration of acetyl-beta-methylcholine *B* was taken two minutes after the subcutaneous injection of acetyl-beta-methylcholine chloride, 20 mg *C* was taken two minutes after the intravenous injection of 0.1 mg of epinephrine hydrochloride which was administered six minutes after the acetyl-beta-methylcholine *D* and *E* were taken four and five minutes, respectively, after epinephrine was given. Note the absence of ectopic ventricular beats.

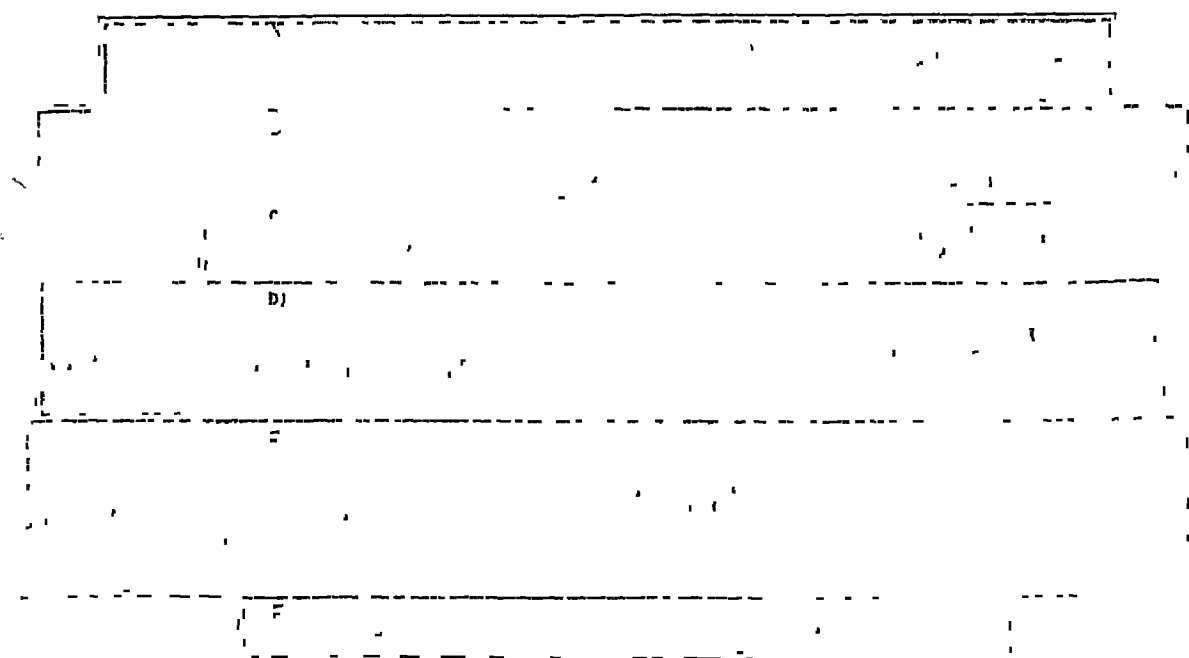


Fig 12 (S D) —Lead II *A* was taken before epinephrine was given. The lower strips were taken thirty seconds, one, two, three and five minutes, respectively, after the intravenous injection of 0.1 mg of epinephrine hydrochloride. *D* and *E* show groups of rapid ectopic ventricular beats.

various barbiturates afforded considerable protection against these irregularities. The doses used, however, were larger than those which can be administered to man. In 1 patient the intravenous injection of sodium amytal, 0.25 Gm., resulted in sound sleep. The administration of epinephrine at this time induced ectopic ventricular beats similar to those of the control record.

*Action of Quinidine on the Vagus Nerve*—There is a further action of quinidine which is of practical interest in this connection. Quinidine acts directly on the myocardium and is a powerful cardiac depressant. The activity of the sinus node is definitely depressed. Although the evidence is against Allbutt's conception of death by vagus inhibition of the heart, the possibility that this mechanism may operate in some cases

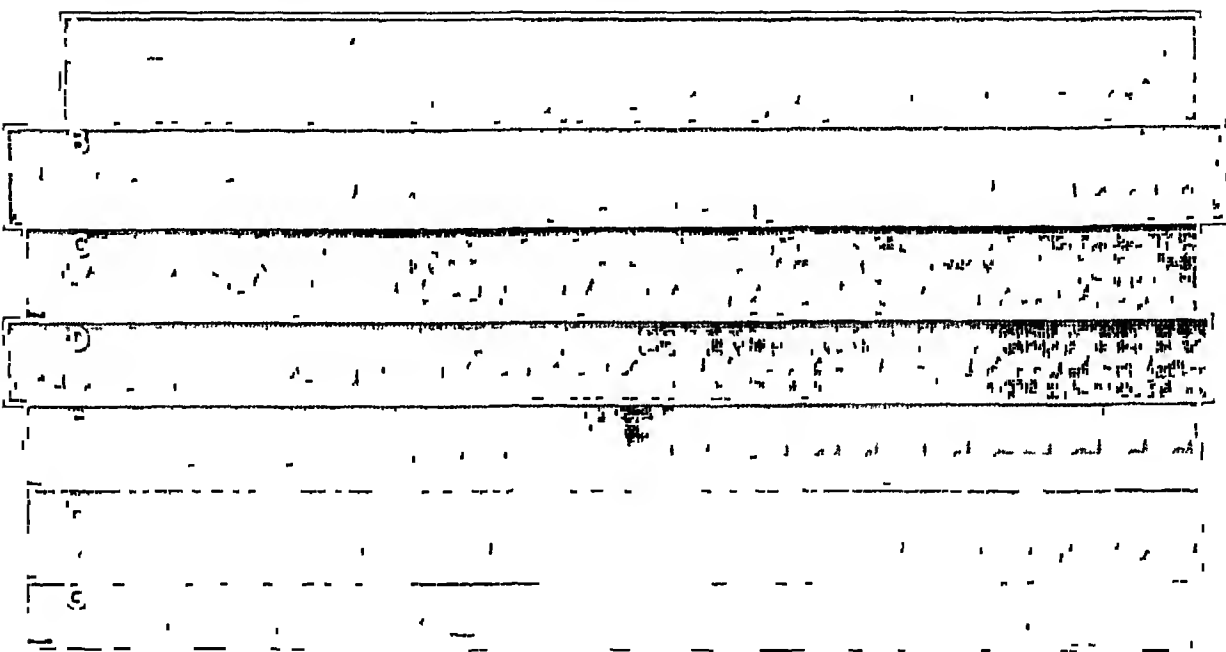


Fig 13 (S D) —Lead II. A is the control record taken seven minutes after the subcutaneous injection of 20 mg of acetyl-beta-methylcholine chloride. At this time epinephrine hydrochloride, 0.1 mg., was injected intravenously, and the lower strips form part of a continuous record taken over a period of five minutes after the injection of epinephrine hydrochloride. Compare with figure 12 and note that the acetyl-beta-methylcholine prevented the development of ectopic ventricular beats.

cannot be absolutely excluded. From this standpoint quinidine may be considered harmful, for the action of a sensitive vagus nerve on a sinus node depressed by quinidine tends to favor permanent cardiac standstill. However, Lewis and his associates<sup>19</sup> have demonstrated in dogs that in addition to its direct cardiac action, quinidine possesses also a powerful

<sup>19</sup> Lewis, T., Drury, A. N., Ilescu, C. C., and Wedd, A. M. Observations Relating to the Action of Quinidine upon the Dog's Heart, *Heart* 9 55, 1921.



vagoparetic effect Dale<sup>20</sup> showed in cats that the effect of the vagus nerve on the sinus node was completely eliminated by quinidine. In a previous study<sup>21</sup> a similar action was demonstrated in man. Six subjects were selected in whom pressure over the carotid sinus produced an intense vagal effect on the sinus node, with prolonged cardiac standstill (fig 13). After the administration of quinidine sulfate, from 1.8 to 2.2 Gm in divided doses, the effect of the reflex stimulation of the vagus nerve was so reduced that only slight slowing of the heart was obtained. Thus quinidine by its direct action on the ventricular muscle lessens the tendency to ventricular fibrillation and by its vagoparetic effect tends to prevent vagal inhibition of the heart.

#### PRACTICAL APPLICATIONS

*Cardiac Standstill*—Studies on the action of drugs on induced cardiac standstill demonstrate that the various sympathomimetic amines are applicable in the treatment of ventricular standstill such as occurs

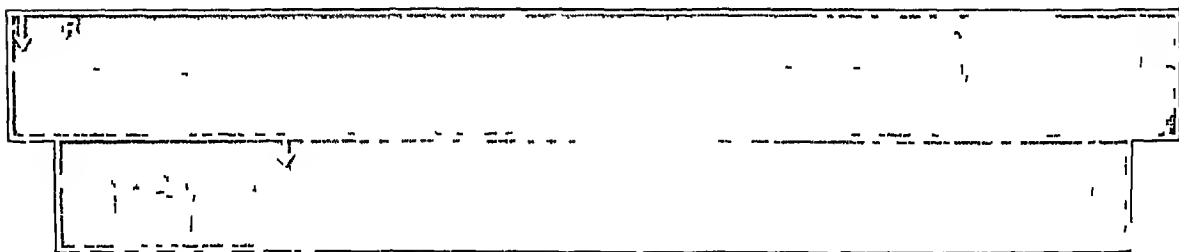


Fig 14 (J Q)—The upper strip shows cardiac standstill of eleven seconds induced by pressure on the right carotid sinus (arrow). The lower strip was taken after the administration of quinidine sulfate, 2.2 Gm. Pressure on the carotid sinus produced only slight vagus stimulation, slowing of the heart rate from 80 to 58 per minute.

in cases of heart block. Substances unrelated to epinephrine in chemical structure and in physiologic action will almost certainly be ineffective. Epinephrine is the most active compound and should be used when syncopal attacks are frequent. Experiments on the duration of action by the present method indicate that a subcutaneous injection of 1 mg every three hours will raise the ventricular rhythmicity so that standstill will be prevented. Ephedrine is the most active compound which is effective on oral administration. There is a great variation in the degree to which the human ventricles react to this drug. In some instances 25 mg injected intravenously increased the ventricular rhythmicity, while in other cases 100 mg was required. Thus, if an effect is not

20 Dale, H. H. Note on the Reversal of Vagus Action by Quinidine as Seen in the Heart of the Cat, *Heart* 9:87, 1921.

21 Nathanson, M. H. Modification of Vagus Inhibition of the Heart by Quinidine, *Proc Soc Exper Biol & Med* 31:1234, 1934.

obtained with the usual oral dose, the amount should be increased up to 150 mg. If this is ineffective, it will be necessary to resort to epinephrine by subcutaneous injection.

*Ventricular Fibrillation*—The present studies show that the action of epinephrine on the ventricular myocardium may be modified and that an induced ectopic ventricular rhythm may be prevented by drugs. This provides a basis for the prophylactic treatment of patients who are liable to sudden death. Whether protection is actually afforded in practice and the degree of this protection cannot be evaluated at present. Morawitz and Hochrein<sup>22</sup> used quinidine empirically for the prevention of acute cardiac death. They concluded from a comparison of a series of treated and untreated patients that quinidine lessened the incidence of sudden death. In the past two years quinidine sulfate has been administered as follows: (1) for six or eight weeks following coronary occlusion and (2) in cases of angina pectoris in which there is evidence of hyperirritability of the ventricles, i. e., frequent ventricular extrasystoles. The dose has usually been 0.4 Gm. three times a day. The number of patients observed is too small for the drawing of any final conclusions as to the efficiency of the drug in the prevention of ventricular fibrillation. No harmful effects were observed. This is mentioned because instances of transient ventricular fibrillation have been reported in patients under quinidine therapy<sup>23</sup>. It cannot be assumed definitely that quinidine was responsible for these attacks, as they may have developed spontaneously. Cases have been reported also in which quinidine seemed to prevent attacks of transient ventricular fibrillation<sup>24</sup>. Unfortunately transient ventricular fibrillation is of infrequent occurrence, and there is little opportunity to study the action of drugs in the prevention of this arrhythmia in clinical cases. It seems however, that the strong evidence of the relationship of epinephrine to ventricular fibrillation and the present studies demonstrating the antagonism of quinidine on the action of epinephrine on the ventricular myocardium justify the use of this drug and a study of the results in a series of suitable cases. Further studies are being carried out with acetyl-beta-methylcholine, and it is possible that this drug may be of practical value as a prophylactic measure in cases of ventricular fibrillation.

22 Morawitz, P., and Hochrein, M. Zur Verhütung des akuten Herztodes, *München med. Wchnschr.* **76** 1075, 1929.

23 Davis, D., and Sprague, H. B. Ventricular Fibrillation. Its Relation to Heart Block, *Am. Heart J.* **4** 559, 1929. Kerr, W. J., and Bender, W. L. Paroxysmal Ventricular Fibrillation with Cardiac Recovery in a Case of Auricular Fibrillation and Complete Heart Block While Under Quinidine Therapy, *Heart* **9** 269, 1921.

24 Escamilla, R. F. Report of a Case of Paroxysmal Ventricular Fibrillation in Relation to Quinidine Therapy, *Am. Heart J.* **8** 850, 1933. Dock<sup>12</sup>.

In addition to the use of drugs, there is a possibility that the factors which dispose the ventricles to fibrillation may be modified in other ways. It is clear that the use of all sympathomimetic drugs, such as epinephrine and ephedrine, is contraindicated, since they stimulate the endings of the sympathetic nerves. Cannon has shown that emotional excitement causes a special discharge of epinephrine, with increased activity of the sympathetic system. It is a familiar fact that emotional excitement is a potent exciting factor of the anginal attack. The relationship between the cardiac accelerator innervation and ventricular fibrillation suggests that nervous and emotional stimuli may tend to induce the mechanism which causes the fatal syncope. Therefore, a most important indication in the prevention of sudden death is therapy directed at the nervous and emotional status of the patient. In addition to the use of quinidine, the application of methods which tend to lessen the activity of the sympathetic nervous system appears to be a rational therapeutic procedure.

#### SUMMARY

Structural changes in the heart are usually inadequate to explain either temporary or fatal cardiac syncope.

There are two physiologic mechanisms in the heart which may cause sudden cessation of the circulation: (1) cardiac standstill and (2) ventricular fibrillation. In the present study it was possible to manipulate the human cardiac mechanism: (1) mechanically, producing cardiac standstill by reflex vagus stimulation, and (2) chemically, inducing a prefibrillation state in the ventricles by sympathetic stimulation with epinephrine administered intravenously. It has been demonstrated that both of these physiologic states may be definitely modified by drugs.

Drugs of the epinephrine series in proper dosage will prevent cardiac standstill.

Prefibrillation rhythm may be prevented by the use of quinidine or of acetyl-beta-methylcholine.

Protection of the sympathetic nervous mechanism by general measures is indicated.

These studies suggest an approach by drug therapy and by general measures toward the prevention of cardiac syncope and sudden death.

# EFFECT OF PROLONGED DIETARY RESTRICTION ON PATIENTS WITH CARDIAC FAILURE

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In June 1933 there came to our attention a 14 year old girl who presented features suggesting hypopituitarism, possibly due to prolonged undernutrition. One of the striking findings was sinus bradycardia of 34 per minute. From personal inquiry and a survey of the literature it appeared that cardiologists in general are unaware that prolonged undernutrition may produce such marked bradycardia. Further studies on this patient of various cardiovascular features, such as the blood flow and the response to exercise, indicated that the bradycardia was associated with a favorable functional state of the circulatory system.

That marked bradycardia may be the result simply of prolonged undernutrition was first observed by Benedict and his associates,<sup>1</sup> who also showed that many of the other features which we observed in our patient, such as a low basal metabolic rate (—37 per cent), low blood pressure (80 systolic and 60 diastolic), a diminished intake of fluid (as low as 640 cc a day) and a small output of urine (as low as 270 cc a day), likewise might follow a low food intake, over a prolonged period. Since all these conditions seem eminently desirable in patients with cardiac weakness and since they evidently could be produced simply by prolonged dietary restriction, we began the study of the effect of such dietary management on patients with cardiac disease.

Dietary restriction as a treatment for heart disease is by no means new, empirically it has been employed for many years. As an example may be mentioned the Karell diet, which is essentially a starvation diet and has been widely used purely on an empirical basis for about

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This study was made possible by grants from the Bingham Associates Fund and the Ella Sachs Plotz Foundation.

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1 Benedict, F G, Miles, W R, Roth, P, and Smith, H M. Human Vitality and Efficiency Under Prolonged Restricted Diet, Washington, D C, Carnegie Institution of Washington, 1919.

seventy years Dietary restriction has been a more or less important feature of the management of cardiac failure in the hands of many physicians Thus, J H Pratt, under whom the present investigation was carried out, has for thirty years recommended a restricted diet in association with absolute rest in bed, his procedure being to place the patient on the Kárell diet for several days and then slowly increase the amount of food so that actually for two or three weeks the patient received a meager diet It was our purpose in the present research to determine what, if any, might be the specific objective and measurable advantages of prolonged dietary restriction and whether such a procedure is desirable in fact as well as in theory

The earliest results of this type of treatment were reported as encouraging<sup>2</sup> A summary of our observations up to the beginning of 1935 has been presented elsewhere<sup>3</sup> Also we have reported our observations on two patients with angina pectoris who were submitted to prolonged undernutrition<sup>4</sup> Despite what was considered a sufficient loss of weight in both patients and a significant drop in the basal metabolism in one of the patients there was no objective evidence that the undernutrition was of particular benefit<sup>4a</sup>

#### PROCEDURE AND MATERIAL FOR PRESENT STUDY

The present report deals with observations on six white patients, four men and two women, all but one showing signs of severe congestive heart failure when the studies were begun The one patient who did not show signs of heart failure had syphilitic aortitis with aortic insufficiency, marked cardiac enlargement and angina pectoris and presented a history of recent cardiac failure Of the other five patients, three had senile heart disease, one had concretio cordis and one had

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2 Proger, S H Boston Dispensary Staff Meeting, March 1934

3 Proger, S H, and Magendantz, H The Effect of Prolonged Dietary Restriction on Patients with Cardiac Weakness, *J Clin Investigation* **14** 720, 1935

4 Proger, S H, Minnich, W R, and Magendantz, H The Circulatory Response to Exercise in Patients with Angina Pectoris, *Am Heart J* **10** 511, 1935

4a Master, Jaffe and Dack, apparently with the view chiefly of lowering the level of oxygen consumption, have employed reduction of food in the treatment of patients with disease of the coronary arteries (particularly thrombosis) Their observations form the basis of several recent reports (Master, A M Coronary Artery Thrombosis, with Treatment by Prolonged Rest in Bed and Low Calory Diet Improved Prognosis, *J A M A* **105** 337 [Aug 3] 1935 Master, A M, Jaffe, H L, and Dack, S Low Basal Metabolic Rates Obtained by Low Calorie Diets in Coronary Artery Disease, *Proc Soc Exper Biol & Med* **32** 779, 1935, The Basal Metabolic Rate in a Patient with Coronary Artery Thrombosis When Placed on an Eight Hundred Calorie Diet, *J Mt Sinai Hosp* **1** 263, 1935, Undernutrition in the Treatment of Coronary Artery Disease [Particularly Thrombosis] Effect on the Basal Metabolism and Circulation, *J Clin Investigation* **15** 353, 1936) Our work, done without knowledge of theirs and concerned with heart failure rather than disease of the coronary arteries, revealed many similar results

rheumatic heart disease with mitral stenosis and regurgitation. One of the two women patients was definitely obese before treatment was instituted. The other patients were of average or slightly below average weight. Observations were made of the arterial and venous blood pressures, cardiac rate, velocity of blood flow, cardiac output, respiratory rate, pulmonary ventilation, oxygen consumption, basal metabolic rate, vital capacity, response to exercise, muscle strength, output of urine, intake of fluid, intake and output of nitrogen, output of sodium chloride, erythrocyte and hemoglobin content of the blood and the blood sugar content. In addition, in one case repeated measurements were made of the serum protein, blood cholesterol and blood calcium. In this case also electrocardiograms and roentgenograms were repeatedly made.

Each patient was first treated with absolute rest in bed, morphine and other sedatives as required, the intake of food and fluid usually being unrestricted. After a sufficient period of time under this regimen had elapsed so that the patient's condition seemed stationary and a fairly good control period was established, digitalis was added to the treatment, all other conditions remaining fixed. Observations could then be made on the isolated effect of digitalis. When another stationary period was reached with digitalis added to the treatment and observations had been made during a sufficiently long period, dietary restriction was instituted, all other conditions again remaining fixed. In this manner, it seemed to us that we were able to separate those changes in the cardiovascular state which were due to the dietary restriction from the beneficial effects of rest in bed, sedatives and digitalis. At first a diet calorically equivalent to the Karell diet<sup>5</sup> was given, and the intake of fluid and salt was unrestricted. As previously noted, the Karell diet has been recognized for many years as being beneficial in the presence of heart failure. Whether this favorable effect is due to the restriction of calories, fluid protein or salt is not known, the diet being limited in all respects. It was our purpose to limit only the calories, so as to determine the influence of this factor alone. Since the diet as we employed it contained only 356 calories,<sup>6</sup> there was obviously a deficiency of protein (carbohydrate, 48 Gm, protein, 32 Gm, and fat, 4 Gm). However, a negative protein balance is a necessary accompaniment of rapid loss of weight in a person of normal size.<sup>7</sup> In fact, it may be that many of the changes which we observed were due to the loss of protein, though convincing evidence points contrariwise.<sup>8</sup>

After one or two weeks the diet was increased to contain about 600 calories (carbohydrate, 80 Gm, protein, 43 Gm, and fat, 13 Gm), and the patient was kept on this diet until the desired loss of weight (about 10 per cent of the body weight) had been obtained, after which the caloric intake was increased sufficiently to maintain a constant weight at the new level. The required intake for this purpose with the patient in bed was from 800 to 1,000 calories. On discharge the patient was allowed 1,200 calories (carbohydrate, 121 Gm, protein, 63 Gm, and fat, 53 Gm). This, though theoretically insufficient, was found to be adequate for maintenance of the low level of weight while there was moderate activity, because patients, particularly the type with which we were dealing, generally are not absolutely rigid in their adherence to a diet.

5 Karell, P. De la cure de lait, *Arch gén de med* **2** 513, 1866

6 Miss Helen Finkelstein, of the Food Clinic, gave valuable assistance in the dietary management in these cases.

7 Jansen, W. H. Untersuchungen über Stickstoffbilanz bei kalorienarmer Ernährung, *Deutsches Arch f klin Med* **124** 1, 1917

8 Lusk, G. The Physiological Effect of Undernutrition, *Physiol Rev* **1** 523, 1921

TABLE 1—The Sample Diets and Menus of the Different Caloric Levels<sup>a</sup>

Sample Menu for One Day									
Food	Total	Carbo- hydrate	Pro- tein	Fat	Calcium	Phos- phorus	Iron	Morning	Night
								Noon	
Diet of 350 Calories									
Skimmed milk	240	12	8	1	0.293	0.230	0.0006	1/2 ounce cottage cheese	1/2 ounce cottage cheese
Meat, fish or chicken	15	12	12	3	0.006	0.112	0.0015	1 serving vegetable	1 serving vegetable
Cottage cheese	35	1	7		0.033	0.255		1/2 slice bread	1/2 slice bread
Bread, whole grain	30	16	3		0.015	0.065	0.0007	1/4 glass skimmed milk	1/4 glass skimmed milk
Vegetables, 5 per cent	200	8	2		0.022	0.032	0.0008	1 serving fruit	1 serving fruit
Fruit, 10 per cent	100	11			0.045	0.021	0.0005	Tea	Tea
Totals		48	32	4	0.469	0.765	0.0041		
Diet of 600 Calories									
Skimmed milk	240	12	8	1	0.293	0.230	0.0006	1 serving fruit	2 ounces meat or fish
Meat, fish or chicken	60	14	14	7	0.003	0.150	0.0020	1/2 ounce cottage cheese	1 serving vegetable
Egg	(1)	6	6	5	0.033	0.090	0.0015	1/2 slice bread	1/2 ounce cottage cheese
Cottage cheese	45	2	9		0.112	0.366		1/2 glass skimmed milk	1/2 slice bread
Bread, whole grain	15	24	4		0.022	0.082	0.0011	1/4 glass milk	1/4 glass milk
Vegetables, 5 per cent	200	8	2		0.022	0.032	0.0008	1 serving fruit	1 serving fruit
Fruit, 10 per cent	300	33			0.135	0.063	0.0015	Tea	Tea
Totals		80	43	13	0.625	1.0492	0.0075		
Diet of 800 Calories									
Skimmed milk	240	12	8	1	0.293	0.230	0.0006	1 serving fruit	3 ounces meat or fish
Meat, fish or chicken	90	22	22	10	0.012	0.225	0.0040	1/2 ounce cottage cheese	1 1/2 servings vegetable
Egg	(1)	6	6	5	0.033	0.090	0.0015	1 slice bread	1/2 ounce cottage cheese
Cottage cheese	45	2	9		0.112	0.366		1/4 glass skimmed milk	1 slice bread
Bread, whole grain	90	48	9		0.045	0.196	0.0021	1 serving fruit	1/4 glass skimmed milk
Vegetables, 5 per cent	300	12	3		0.033	0.078	0.0012	Tea	1 serving fruit
Fruit, 10 per cent	300	33			0.135	0.063	0.0015		Tea
Totals		107	57	16	0.663	1.248	0.0099		
Diet of 1,095 Calories									
Milk	360	18	12	15	0.432	0.394	0.0039	1 serving fruit	4 ounces meat or fish
Meat, fish or chicken	120	27	27	14	0.016	0.300	0.0040	1 teaspoon butter	1 1/2 servings vegetable
Egg	(1)	6	6	5	0.033	0.090	0.0015	1 slice bread	1 teaspoon butter
Bread, whole grain	90	48	9		0.045	0.196	0.0021	1/2 glass milk	1 slice bread
Vegetables, 5 per cent	300	12	3		0.033	0.078	0.0012	1 serving fruit	1/2 glass milk
Fruit, 10 per cent	300	33		13	0.135	0.063	0.0015	Tea	1 serving fruit
Butter	15				0.002	0.003			Tea
Totals		111	57	17	0.696	1.064	0.0112		
Diet of 1,200 Calories									
Milk	480	24	16	20	0.576	0.445	0.0012	1 serving fruit	4 ounces meat or fish
Meat, fish or chicken	120	27	27	14	0.016	0.300	0.0040	1 teaspoon butter	2 servings vegetables
Egg	(1)	6	6	5	0.033	0.090	0.0015	1 slice bread	1 teaspoon butter
Bread, whole grain	90	48	9		0.045	0.196	0.0021	1/2 glass milk	1 slice bread
Vegetables, 5 per cent	400	16	4		0.044	0.104	0.0016	1 serving fruit	1/2 glass milk
Fruit, 10 per cent	300	33		13	0.135	0.063	0.0015	Tea	1 serving fruit
Butter	15				0.002	0.003			Tea
Totals		121	62	32	0.851	1.201	0.0119		

<sup>a</sup> Normal mineral requirement for an adult calcium 0.65 Gm phosphorus 1.2 Gm iron 0.015 Gm per day

While in the hospital each patient was kept at absolute rest in bed, being allowed bathroom privileges only during the latter part of his stay. The patient was taken to the laboratory in the morning, where all tests were made under basal conditions. During these tests the patient was in a semirecumbent position. Observations were made of the basal metabolic rate both with the Benedict-Roth and with the Tissot spirometer. The basal metabolic rate was calculated according to the Aub-Du Bois standards. The observations during exercise were made in the afternoon, from three to four hours after the noon meal. Exercise consisted of pedaling on a stationary bicycle of the Prony-brake type at a fixed rate against a constant pull. During exercise observations were made on the pulse rate, respiratory rate and respiratory minute volume and in one case on the oxygen consumption.

The acetylene method of Grollman<sup>9</sup> was used to measure the cardiac output and the decholin method of Winternitz, Deutsch and Brull<sup>10</sup> was used for measuring the velocity of the blood flow. At the time the measurements of the cardiac output were made the degree of pulmonary congestion was not so great as to interfere with the obtaining of samples of true alveolar air<sup>11</sup>. In three of the cases repeated measurements were considered unsatisfactory owing to a lack of cooperation. The venous pressure was measured by a modified Moritz-Tabora method<sup>12</sup>. The size of the heart was traced from roentgenograms taken at a distance of 2 meters, with the patient standing. The area was measured with a planimeter, as suggested by Levy<sup>13</sup>. The heart rate, which was counted for a full minute at the apex and the blood pressure, which was measured also by auscultation, were taken twice within a period of about five minutes. The lower values are recorded.

The various chemical measurements were made according to the methods of Hagedorn and Jensen<sup>14</sup> (blood sugar), Clark and Collip<sup>15</sup> (serum calcium), Howe<sup>16</sup> (blood sugar) and Folin and Denis<sup>17</sup> (urinary nitrogen) and by Oser

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9 Grollman, A. The Determination of the Cardiac Output of Man by the Use of Acetylene, *Am J Physiol* **88** 432, 1929.

10 Winternitz, M., Deutsch, J., and Brull, Z. Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholinjektion, *Med Klin* **27** 986, 1931.

11 Grollman, A., Proger, S. H., and Dennig, H. Zur Bestimmung des Minutenvolumens mit der Azetylenmethode bei Arbeit, bei normalen und kranken Menschen, *Arch f exper Path u Pharmacol* **162** 463, 1931.

12 Griffith, G. C., Chamberlain, C. T., and Kitchell, J. R. A Simplified Apparatus for Direct Venous Pressure Determination Modified from Moritz and v Tabora, *Am J M Sc* **187** 371, 1934.

13 Levy, R. L. The Size of the Heart in Pneumonia, *Arch Int Med* **32** 359 (Sept) 1923.

14 Hagedorn, H. C., and Jensen, B. N. Zur Mikrobestimmung des Blutzuckers mittels Ferricyanid, *Biochem Ztschr* **135** 46, 1923, **137** 92, 1923.

15 Clark, E. P., and Collip, J. B. A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, *J Biol Chem* **63** 461, 1925.

16 Howe, P. E. The Determination of Proteins in Blood. A Micro Method, *J Biol Chem* **49** 109, 1921.

17 Folin, O., and Denis, W. Nitrogen Determinations by Direct Nesslerization, *J Biol Chem* **26** 473, 1916.



and Karr's<sup>18</sup> modification of the method of Myers and Wardell<sup>19</sup> (blood cholesterol)

#### REPORT OF CASES

CASE 1—G W, a man aged 68, had had increasing dyspnea on exertion for three years. In the past two years there had also been slight substernal pain on exertion, which was relieved by rest. No pain had been noted in the few months before the patient's admission to the hospital. In the year before the studies were begun he was admitted three times to the Boston City Hospital with congestive heart failure. Examination showed slight orthopnea, cyanosis, considerable cardiac enlargement, regular action of the heart, a heart rate of 80, hepatic engorgement (the edge of the liver was 4 cm below the costal margin in the right midclavicular line) and moderate pretibial pitting edema. Roentgenograms confirmed the diagnosis of a markedly dilated heart. An electrocardiogram showed partial auriculoventricular block (P R interval, 0.25 second) and left bundle branch block. There was considerable improvement after rest in bed and digitalis therapy. The subsequent changes are noted in table 2.

CASE 2—M A, a man aged 48, as long as nine years before his admission to the hospital had noted some nocturnal edema about the ankles. The condition had gradually become more noticeable. In the past four or five years there had been increasing dyspnea on exertion. In the past year there had been orthopnea, which in the few weeks before the patient's admission to the hospital had become extreme, being accompanied by a constant nonproductive cough. Examination showed moderate orthopnea, slight cardiac enlargement and rapid auricular fibrillation. The pulse rate was 114, with a deficit of 20. The blood pressure was 130 systolic and 88 diastolic. There were moist râles at the bases of both lungs. The edge of the liver was felt 8 cm below the costal margin, and there was moderate pretibial pitting edema. Roentgenograms showed evidence of a calcified pericardium (etiology not determined after careful inquiry), slight cardiac enlargement and bilateral slight pleural effusion. An electrocardiogram showed only low voltage and auricular fibrillation. There was only slight improvement until digitalis was given on the tenth day, after which the orthopnea, edema and pulmonary congestion disappeared. The size of the liver did not diminish considerably, and it was still at least 4 cm below the costal margin when the patient was discharged after dietary restriction. The changes following dietary restriction are recorded in table 2.

CASE 3—L McM, a woman aged 50, was admitted to the hospital only two weeks after the sudden onset of dyspnea, epigastric distress, palpitation and general weakness. In the two weeks before her admission to the hospital the symptoms had become progressively more severe. During the week preceding the onset of symptoms she had performed an unusually great amount of physical work. There had been no infection. There was no previous history of rheumatic infection. Examination showed moderate orthopnea, slight cyanosis, considerable cardiac enlargement to the right and left, a mitral diastolic murmur with a booming first sound, rapid auricular fibrillation (120) with a moderate pulse deficit, moist râles at the bases of both lungs with evidence of pleural effusion on the right, hepato-

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18 Oser, B L, and Karr, W G. The Lipoid Partition in Blood in Health and in Disease, *Arch Int Med* **36** 507 (Oct) 1925.

19 Myers, V C, and Wardell, E L. The Colorimetric Estimation of Cholesterol in Blood, with a Note on the Estimation of Coprosterol in Feces, *J Biol Chem* **36** 147, 1918.

TABLE 2—Data on the Changes Noted Following Dietary Restriction \*

Patient	Sex	Age, Years	Weight, Kg		Height, Cm	Surface Area, Sq Cm		Heart Rate per Minute		Blood Pressure				Velocity of Blood Flow, Seconds		Vital Capacity, Cc		Respiratory Rate per Minute		Respiratory Minute Volume, Liters		Basal Metabolic Rate, Percentage		Oxygen Consumption, Cc per Min		Decrease in Oxygen Consumption, Percentage		Arteriovenous Oxygen Difference, Cc per Liter		Cardiac Output per Sq M Surface Area, Liters per Min		Stroke Output, Cc per Beat		
			Before	After		Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	
M A	M	48	69.0	59.0	165	1.75	1.63	73	50	110	70	100	60	22	23	3,350	3,725	18	13	6.5	4.9	—7	—14	211	176	17	61	56	11	3.7	2.3	2.3	56	71
G W	M	68	64.8	54.0	165	1.70	1.57	72	59	126	86	110	70	27	25	2,450	2,900	12	9	5.9	5.3	+4	—6	217	180	16	63	66	3.4	2.8	2.0	1.8	47	47
M W	M	60	64.8	58.4	163	1.69	1.61	59	45	140	42	140	36	30	33	3,100	3,550	17	13	8.4	5.9	+31	+2	276	205	26								
F C	M	67	69.7	62.2	171	1.80	1.72	61	46	174	87	154	74	29	24	3,300	4,050	12	9	6.9	4.9	+5	—17	231	175	24	57	47	4.2	3.7	2.3	2.2	70	80
Average		61	67.1	58.1	166	1.74	1.63	66	50	138	71	126	60	27	26	3,050	3,550	15	11	6.9	5.3	+8	—9	234	184	21	60	56	3.9	3.3	2.2	2.1	58	67
McM	F	50	54.5	49.3	140	1.40	1.34	74	73	130	74	128	72	24	23	2,150	2,400	22	20	6.7	6.0	—9	—8	175	170	8								
C M	F	57	67.3	58.8	148	1.60	1.51	81	70	150	86	120	74	40	35	800	1,200	20	17	7.3	5.7	+16	+11	234	200	14								

\* The averages given are for the four cases in which the changes were most striking

megaly (the edge of the liver being 2 cm below the costal margin) and slight pretibial pitting edema. There were no signs of hyperthyroidism. She responded well to thoracentesis, rest in bed with sedatives and digitalis, the further effect from dietary restriction being slight (table 2).

CASE 4—C M, a woman aged 57, had her first period of congestive heart failure two years before her admission to the hospital. After satisfactory treatment at that time she was comfortable with moderate restriction of activities until two months before her admission to the hospital, since when there had been increasing dyspnea on exertion, coughing and increasing edema of the lower extremities. Examination showed moderate obesity, orthopnea, marked cyanosis, marked pitting edema of the lower extremities and extending up to the lower part of the back, considerable cardiac enlargement to the right and left, a loud, rough apical systolic murmur, an accentuated second pulmonic sound, rapid auricular fibrillation, a blood pressure of 146 systolic and 90 diastolic, moist râles over the bases of both lungs and hepatomegaly, the edge of the liver being 5 cm below the costal margin in the right midclavicular line. The clinical condition was moderately improved with rest in bed and sedatives followed by diuretics (salyrgan) and digitalis. There was definite though not striking further improvement with dietary restriction. After the effect had been noted of reducing the patient's weight from an overweight to a normal level, an attempt was made to study further the effect of reducing the weight to an underweight level. She refused to cooperate, however, and the weight was not reduced below the average level.

CASE 5—M W, a man aged 60, first noted abnormal dyspnea on exertion seven years before his admission to the hospital. At that time he was known to have syphilitic heart disease. For six years he had had substernal pain on exertion, particularly in the winter, which was regularly relieved by rest or glyceryl tri-nitrate therapy. He had irregular antisyphilitic treatment during this entire period. About six weeks before his admission to the hospital he had early signs of congestive heart failure which disappeared in a few weeks after rest in bed, sedatives and digitalis therapy. At the time of his admission to the hospital there were no signs of congestive heart failure. There were peripheral signs of aortic insufficiency. The heart was considerably enlarged to the left. There were diastolic and systolic blowing murmurs over the aortic area. The blood pressure was 180 systolic and 40 diastolic. This patient did not receive digitalis. The changes noted in table 2 followed a preliminary control period of simple rest in bed.

CASE 6—F C, a man aged 67, first noticed increasing dyspnea on exertion three months before his admission to the hospital. There was also increased coughing. Within two months marked orthopnea and probably some edema of the lower extremities were noted. The symptoms became progressively worse until the patient's admission to the hospital, when he was found to have marked orthopnea, Cheyne-Stokes respiration, alternating pulse, moderate cyanosis, pleural effusion on the right side, many medium-sized moist râles over the bases of both lungs, considerable cardiac enlargement, a cardiac rate of 100, a faint apical systolic blow, a blood pressure of 166 systolic and 110 diastolic, hepatomegaly (the edge of the liver was 5 cm below the costal margin in the right midclavicular line) and slight pretibial pitting edema. He was irrational. Roentgenograms showed considerable cardiac enlargement with pleural effusion on the right. The electrocardiogram showed left axis deviation and inverted T waves in leads I and II. He did not seem to improve considerably with rest and morphine therapy alone. His condition was so serious that a Karell diet was given for four days. By

thoracentesis of the right side 1,000 cc of fluid was removed. After thirteen days there was enough improvement so that studies could be begun. Subsequent data are given in figure 1.

### RESULTS

In general the results were considered distinctly favorable in four of the six patients, the four men. In these the improvement in the cardiovascular state and the degree of diminution of the level of energy metabolism were out of proportion to the loss of weight. In the one obese woman whose weight was reduced from an overweight level to an average level<sup>20</sup> the corresponding changes were only proportional, thus, for example, with a loss of 18.5 per cent in body weight to an average level there was a corresponding fall in oxygen consumption of 17 per cent. In the other woman there were only slight functional changes which could be attributed to reduction of the weight to an underweight level.

In figure 1 are presented representative results in one of the four men. These may be taken as characteristic of what can be expected from the regimen as outlined. It will be seen that a loss of 16 pounds (7.3 Kg), from 153 pounds (69.5 Kg) to 137 pounds (62.2 Kg), took place in about forty days. During the first thirty-six days of observation<sup>21</sup> the average daily intake of food was 2,320 calories, during the next nine days, 360 calories, during the next thirty-eight days, 600 calories, and thereafter, 800 calories. Digitalis was administered daily for fourteen days beginning with the twenty-third day, the total amount being 5 Gm of the powdered leaf. This produced no subjective discomfort, though there were signs of delayed auriculoventricular conduction and depression of the ST interval in leads I and II. As may be seen in the figure, the effects directly attributable to digitalis were the slowing of the heart rate (in the presence of sinus rhythm) from about 72 to about 60 per minute, a moderate elevation of the systolic blood pressure (this effect only in this patient), an increase in the vital capacity of 600 cc from the time when digitalis was given or 300 cc from a previous high level, a slight decrease in the respiratory rate and in the respiratory minute volume and an increase in the cardiac output accompanied with a decrease in the arteriovenous oxygen difference.

<sup>20</sup> Metropolitan Life Insurance Company tables.

<sup>21</sup> This patient was in the hospital for thirteen days before the data recorded on the chart were obtained. His condition was so serious that the intake of fluid had to be restricted. For four days he was on a Karel diet. During this period thoracentesis was performed, and 1,000 cc of fluid was removed from the right pleural cavity. There was a loss of 21 pounds (9.5 Kg), from 179 pounds (81.5 Kg) to 158 pounds (71.7). The results recorded in figure 1, therefore, do not represent the maximum change in this patient from the level of the most extreme heart failure.

The results of dietary restriction may be noted as a considerable slowing of the heart rate (from about 60 to 46 per minute), a drop in both the systolic and the diastolic blood pressure (from about 174 millimeters of mercury systolic and 88 diastolic to 154 systolic and 74 diastolic), a slight increase in the velocity of blood flow, a definite increase in the vital capacity (from 3,300 to 4,100 cc), a decrease in the respiratory rate (from 12 to 9 per minute, with a decrease in the respiratory minute volume, from about 7 to about 5 liters per minute), a drop of 24 per cent in the oxygen consumption (from about 230 to 175 cc per minute, representing a decrease in the basal metabolic rate from +5 to -17 per cent), and a decrease in the cardiac output (about 0.5 liter per minute), associated first simply with lowering of the oxygen consumption and later also with a decrease in the arteriovenous oxygen difference.

The height of the venous pressure is not recorded in the figure, since it was normal even before digitalis was given, having dropped to 53 mm of water after absolute rest in bed and the administration of morphine. The fluctuation thereafter was between 53 and 72 mm of water.

No change was observed in the electrocardiograms taken at frequent intervals throughout the period of observation.

There was definite roentgenographic evidence of a decrease in the size of the heart as the result first of digitalis and then of the dietary restriction (fig 2). This is illustrated in figure 3 in a manner employed by Levy<sup>13</sup> and Stewart and Cohn.<sup>22</sup>

There was no important difference in the response of the heart rate to atropine (0.65 mg of atropine sulfate injected subcutaneously) before and after the slowing due to the diet.

According to the formula of Evans and Matsuoka,<sup>23</sup> in which the work of the heart is measured largely by the product of the cardiac output and the mean arterial pressure, the work of the heart in this patient was considerably diminished by the diet (from 7.5 to 5.7 kilogrammeters of work per minute), since both the cardiac output and the mean arterial pressure became smaller.

Because patients occasionally complain of weakness following the restriction of food, the strength of the grip was measured in each hand with a dynamometer on many occasions before and during the period of dietary restriction. There was no noticeable change in the muscular strength as measured in this manner.

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22 Stewart, H. J., and Cohn, A. E. Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart, *J. Clin. Investigation* **11** 917, 1932.

23 Evans, C. L., and Matsuoka, Y. The Effect of Various Mechanical Conditions on the Gaseous Metabolism and Efficiency of the Mammalian Heart, *J. Physiol.* **49** 378, 1915.

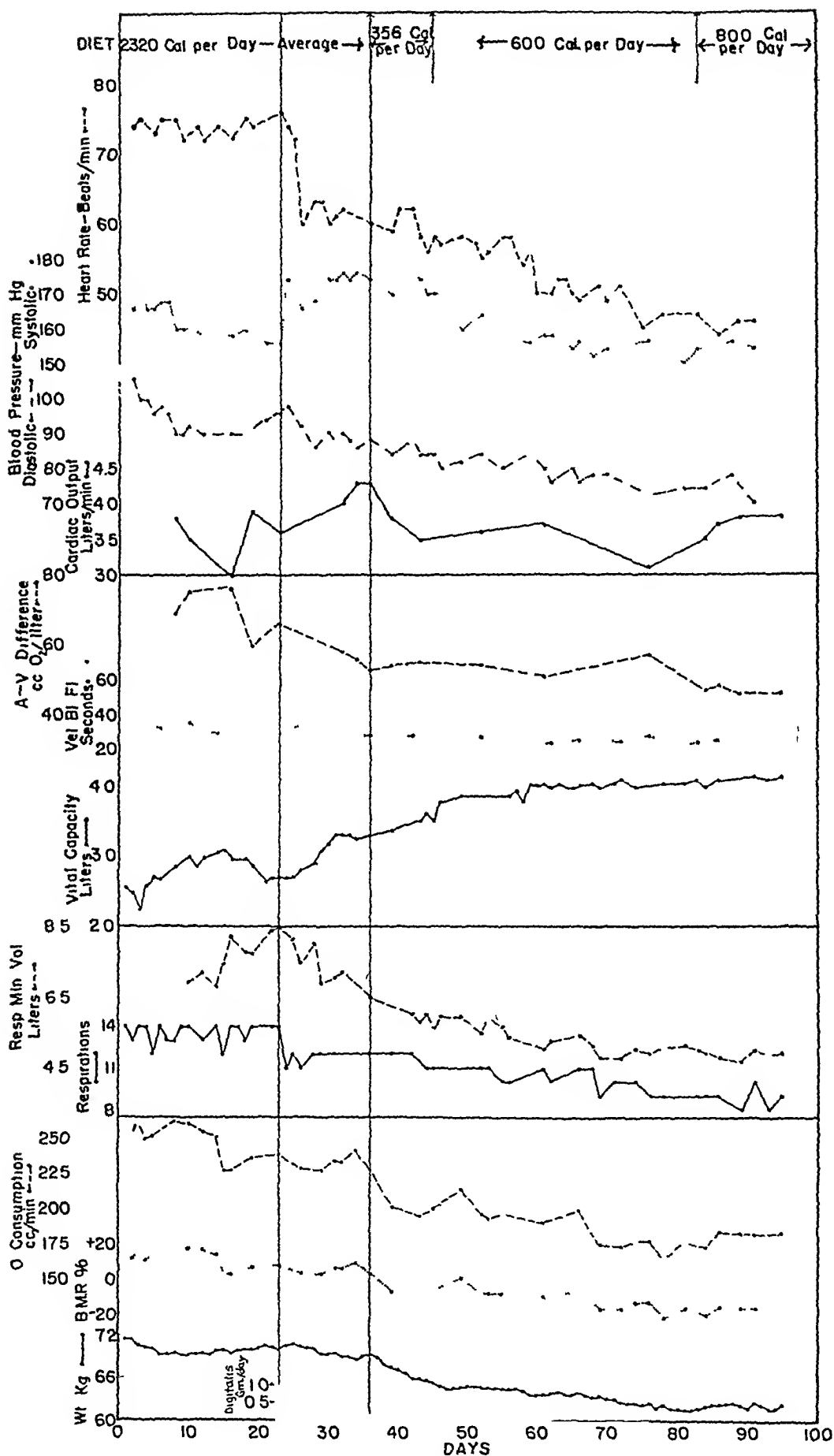


Fig 1—Representative results in patient F C, showing the changes noted before digitalis was given, after digitalis was given and after dietary restriction. Pulsus alternans and Cheyne-Stokes' respiration, both of which were present at the onset, disappeared on the second day after digitalis was given and on the tenth day after dietary restriction was begun, respectively.



Fig 2—Teleoroentgenograms taken of F C (A) before any treatment was given, (B) before digitalis treatment, (C) after digitalis treatment and (D) after dietary restriction

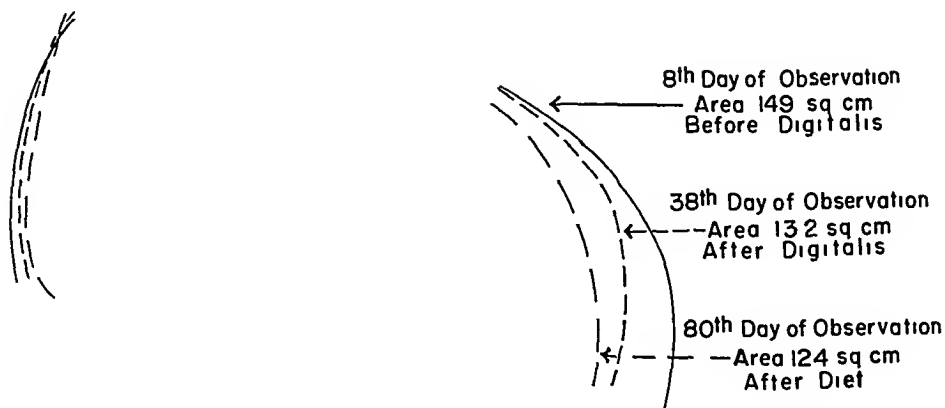


Fig 3—A comparison of the surface areas of the shadow of the heart in F C before digitalis therapy, after digitalis therapy and after dietary restriction

In table 2 are grouped the observations on all the patients of the corresponding features, mainly cardiovascular, recorded in figure 1. The changes as given represent those directly attributable to dietary restriction. The values given represent averages over from three to five days. In general it will be seen that in the four men the changes corresponded to those just presented and detailed in the single illustrative case. There was an average loss of weight of 12 per cent, from 147 pounds (66.8 Kg.) to 129 pounds (58.7 Kg.), with a variation from 9.8 per cent to 16.7 per cent. There was evidently no relationship between the extent of the changes and the magnitude of the loss of weight. The average decrease in the heart rate was from 66 to 50 per minute, the variations being from 23 per minute (73 to 50) to 13 per minute (72 to 59).

The average blood pressure, both systolic and diastolic, dropped (from 130 systolic and 71 diastolic to 126 systolic and 60 diastolic). In only one of the patients (M. W.) was there no significant change.

There appeared to be no definite change in the velocity of blood flow, although in one patient (F. C.) there was perhaps a slight increase. The average time required for decholin to reach the taste buds of the tongue from the cubital vein was twenty-seven seconds before and twenty-six seconds after the institution of dietary restriction.

There was a definite and regular increase in the vital capacity, varying from 375 to 750 cc., the average increase being from 3,050 to 3,550 cc.

The respiratory rate diminished almost equally in the four patients, the average being from 15 to 11 per minute. The average respiratory minute volume likewise was considerably smaller after the restriction of food, the average change being from 6.9 to 5.3 liters per minute.

The average fall in oxygen consumption per minute from 237 to 184 cc. represented a more or less uniform change in the four patients. This represented an average drop of 22 per cent. The average decrease in the basal metabolic rate, however, was only 17 per cent (from +8 to -9 per cent). This difference is of course due to the fact that the basal metabolic rate is calculated on the basis of the intake of oxygen per square meter of surface area, and with loss in weight the surface area becomes reduced. If the oxygen consumption diminished in accordance with the diminution in the surface area the basal metabolic rate would in fact be unchanged. Thus the decrease in the basal metabolic rate which takes place when weight is lost represents a greater decrease in oxygen intake than when this occurs with no loss or with a gain in weight. For example, in one case (M. A.), in which a loss of weight of 14 per cent was accompanied with a diminution of the surface area of 10 per cent, there was a decrease in the basal metabolic rate of only 7 per cent, whereas the total oxygen consumption decreased 17 per cent.



In the case of M W the initial basal metabolic rate was  $+31$  per cent. In the absence of congestive heart failure (this was the only patient in whom there were no signs of congestive heart failure when the studies were begun), leukemia, fever and other conditions not due to disorder of the thyroid gland which are known to be associated with elevation of the metabolic rate, a basal metabolic rate of  $+31$  per cent suggests the presence of hyperthyroidism. However, careful studies revealed no evidence of increased activity of the thyroid gland. We have observed in several patients with enlargement of the heart an apparently unexplained elevation of the metabolic rate. These cases form the subject of another study to be reported on later.

The average arteriovenous oxygen difference was decreased from 60 to 56 cc per liter. This was associated with a more considerable decrease in oxygen consumption, hence the cardiac output,  $\frac{\text{oxygen consumption}}{\text{arteriovenous oxygen difference}}$ , also was lessened (from 3.9 to 3.3 liters per minute). The average cardiac output per square meter of surface area (cardiac index) was practically unchanged (from 2.2 to 2.1 liters per minute). The values for the cardiac output and the cardiac index were within the normal range as given by Grollman.<sup>24</sup> There was an increase in the stroke output from 58 to 67 cc.

If the work of the heart is calculated according to the formula of Evans and Matsuoka,<sup>23</sup> it is found that the average decrease in work per minute is from 5.8 to 4.2 kilogrammeters, the decrease in work per beat being from 88 to 80 grammmeters.

In three of the men the rest in bed was interrupted a few times each week for the performance for a short period (five minutes) of light exercise on a stationary bicycle. The improvement in the response to exercise after due allowance had been made for the effect of training paralleled the improvement at rest, the decrease following dietary restriction in the pulse rate, respiratory rate and pulmonary ventilation during exercise corresponding proportionately to the decrease at rest noted in table 2. Thus, in the case of M A the apex rate during the last minute of exercise, as nearly as it could be counted, was about 200 per minute, after digitalis therapy was added it was 164 per minute, whereas after dietary restriction the apex rate was only 140 during the last minute of exercise. The corresponding change in the respiratory rate was from 27 to 23 to 20 per minute, the change in the pulmonary ventilation was from 45 to 38 to 23 liters per minute, the oxygen consumption during the last minute of exercise (for procedure and technic see footnote 4) decreased from 1,160 cc per minute before to 1,010 cc after dietary restriction. The oxygen consumption during exercise was measured only in this one patient. In two of the patients

<sup>24</sup> Grollman, Arthur. *The Cardiac Output of Man in Health and Disease*, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

there was a definite improvement in the subjective response to exercise, the patient being able to perform the work with much greater ease. This subjective improvement was not so noticeable in the third patient (M W), largely because he complained so much of weakness during the exercise.

In two of the patients the venous pressure had not reached a normal level before the institution of the special diet. In one (C M) the venous pressure decreased from 174 to 124 mm of water after dietary restriction, in the other (M A), from 120 to 70 mm.

In table 3 may be seen the relationship in F C between the weight, the intake of food, the urinary nitrogen content and the output of urine. The nitrogen in the food was calculated from the protein values as given by Sherman<sup>25</sup>. Analyses of samples of food showed these values to check within 2.2 per cent. The changes chiefly to be noted are the diuresis due to digitalis, though at the time digitalis was given there were no signs of chronic passive congestion, and the negative nitrogen balance as a result of the dietary restriction. Absolute figures for nitrogen balance were not obtained, as the nitrogen in the feces was not measured. Assuming even wide fluctuations in the fecal nitrogen content, a general idea may be gathered of the nitrogen balance from the amount of nitrogen in the food and the urinary nitrogen content. The nitrogen values from table 3 are summarized in table 4, which also contains the values for two other patients, representing two other types of effects of the diet (greater and less loss) on the nitrogen balance. The amount of sodium chloride excreted in the urine also is given in table 4. It is seen that in addition to the loss of nitrogen there was a decrease in the output of sodium chloride, which under the circumstances can be taken to indicate a decrease in the intake of sodium chloride. This decrease in the intake of salt was spontaneous, for there was no restriction, but the decrease was of regular occurrence in all the patients. How important the factors of the loss of nitrogen and the lowered intake of sodium chloride were in the production of the changes noted is impossible for us to determine. It was evident, however, that the magnitude of the changes was not definitely related to the variations in these factors in the different patients. This may be seen clearly in table 4. In the case of M W the loss of nitrogen was greater, whereas in F C it was small, even during the period of most rigid dietary restriction. Yet the effect on the functional state of the cardiovascular system, as well as on the oxygen metabolism was marked in both cases. On the other hand, in the case of L McM, who like F C, showed little loss of nitrogen, the effect of the diet on the circulation was relatively slight.

<sup>25</sup> Sherman, H. C. *The Chemistry of Food and Nutrition*, ed. 4, New York, The Macmillan Company, 1932.

TABLE 3—*Daily Observations of the Weight, Intake of Food and Output of Urine in One Patient*

Day of Observa- tion	Weight, Pounds	Intake of Food				Carbo- hydrate, Gm	Output of Urine, Cc	Output of Nitrogen, Gm
		Calories	Protein, Gm	Nitrogen, Gm	Fat, Gm			
1	158½	2,240	73	11 6	104	253	755	11 9
2	157½	2,603	93	14 8	131	263	740	10 3
3	155½	2,298	93	14 8	106	243	275	4 2
4	155	1,197	54	8 6	65	99	895	11 7
5	154½	1,458	50	8 0	62	175	575	8 5
6	152½	1,949	75	12 0	97	194	580	8 8
7	152½	2,435	103	16 4	119	238	800	10 6
8	153	1,618	68	10 8	82	152	660	9 2
9	152½	1,921	71	11 1	101	182	705	10 2
10	152½	2,501	104	16 6	129	231	715	11 0
11	153	2,081	67	10 7	89	253	665	11 0
12	153	1,662	66	10 5	74	183	870	10 3
13	152½	2,810	102	16 3	146	272	805	10 1
14	154	2,469	99	15 8	153	299	680	7 2
15	154¼	2,483	78	12 4	111	268	665	7 3
16	153	2,506	79	12 6	134	246	450	5 8
17	154	2,898	94	13 4	152	286	1,005	12 7
18	154¼	1,762	66	10 5	74	208	810	9 9
19	154¼	2,507	80	12 8	131	252	565	6 3
20	154½	2,607	93	14 7	123	282	410	4 4
21	155½	2,929	77	12 3	153	311	505	6 3
22	155	1,877	68	10 8	77	183	500	6 5
23	154¼	2,437	85	13 6	113	270	640	7 5
24	155½	2,464	84	13 4	112	280	580	6 6
25	156	1,980	67	10 7	96	212	920	9 3
26	155	1,866	70	11 2	90	194	1,295	10 0
27	154½	2,659	85	13 6	127	294	1,165	9 6
28	154½	2,709	92	14 4	129	295	1,340	6 7
29	153	2,573	76	12 1	113	313	815	7 2
30	153	2,393	80	12 8	114	263	735	7 8
31	153	1,829	71	11 3	85	195	825	8 4
32	152	2,003	77	10 7	103	102	575	7 1
33	152	2,799	87	13 9	127	327	615	8 6
34	151½	2,947	93	15 6	147	308	510	8 5
35	152½	2,583	96	15 3	123	273	705	11 1
36	152¾	2,147	69	11 0	114	211	1,045	12 1
37	152	356	32	5 13	4	48	1,200	9 0
38	151	356	32	5 13	4	48	905	7 2
39	149	356	32	5 13	4	48	630	7 6
40	148	356	32	5 13	4	48	500	7 5
41	147	356	32	5 13	4	48	570	9 2
42	145¾	356	32	5 13	4	48	565	5 3
43	145½	356	32	5 13	4	48	650	6 8
44	145¼	356	32	5 13	4	48	800	6 2
45	144	278	26	4 16	2	39	455	4 6
46	143	601	43	6 88	13	78	385	5 9
47	142½	601	43	6 88	13	78	475	7 6
48	142½	601	43	6 88	13	78	490	6 9
49	142¾	601	43	6 88	13	78	420	5 5
50	143	601	43	6 88	13	78	1,110	10 1
51	143	601	43	6 88	13	78	635	6 2
52	142½	601	43	6 88	13	78	854	7 7
53	142½	601	43	6 88	13	78	815	8 1
54	141½	601	43	6 88	13	78	440	5 3
55	142	601	43	6 88	13	78	680	7 6
56	142	601	43	6 88	13	78	775	7 7
57	142	601	43	6 88	13	78	955	5 9
58	141	601	43	6 88	13	78	795	6 8
59	140½	601	43	6 88	13	78	555	4 9
60	140½	601	43	6 88	13	78	445	4 7
61	140½	601	43	6 88	13	78	425	5 9
62	140¾	601	43	6 88	13	78	580	5 0
63	141	601	43	6 88	13	78	425	3 9
64	140½	601	43	6 88	13	78	670	6 7
65	140½	601	43	6 88	13	78	760	5 1
66	141	609	43	6 88	13	80	695	4 7
67	139¾	609	43	6 88	13	80	480	4 1
68	139½	609	43	6 88	13	80	830	5 4
69	139¾	609	43	6 88	13	80		
70	139	609	43	6 88	13	80	935	5 7
71	139	609	43	6 88	13	80	660	3 3
72	138	609	43	6 88	13	80	540	4 5
73	137½	609	43	6 88	13	80	750	5 3
74	137½	609	43	6 88	13	80	965	4 8
75	137	609	43	6 88	13	80	1,140	7 2
76	137½	609	43	6 88	13	80	1,135	6 7

TABLE 3—Daily Observations of the Weight, Intake of Food and Output of Urine in One Patient—Continued

Day of Observation	Weight, Pounds	Intake of Food				Carbo-hydrate, Gm	Output of Urine, Cc	Output of Nitrogen, Gm
		Calories	Protein, Gm	Nitrogen, Gm	Fat, Gm			
77	136½	609	43	6.88	13	80	965	5.4
78	137	609	43	6.88	13	80	935	5.3
79	136¼	609	43	6.88	13	80	915	5.4
80	136	609	43	6.88	13	80		
81	135½	609	43	6.88	13	80	715	6.1
82	136	609	43	6.88	13	80	635	9.0
83	136¾	800	57	9.12	16	107	1,035	6.6
84	137	800	57	9.12	16	107	750	7.4
85	137	800	57	9.12	16	107	870	6.7
86	137	800	57	9.12	16	107	910	5.9
87	137½	800	57	9.12	16	107	1,185	7.1
88	137½	800	57	9.12	16	107	1,010	6.3
89	137	800	57	9.12	16	107	905	5.8
90	136¾	800	57	9.12	16	107	660	6.2
91	137½	800	57	9.12	16	107	920	6.2
92	137	800	57	9.12	16	107	1,150	7.1

Both F. C. and L. McM. had been for at least one week under extreme dietary restriction, because of the seriousness of their condition before our observations were begun. This probably accounts for the positive nitrogen balance before the period of dietary restriction.<sup>8</sup> The unusually great loss of nitrogen in the case of M. W. was unquestionably due to the abnormally elevated basal metabolic rate.

The loss of nitrogen was observed also in the obese patient, being approximately the same as that recorded for L. McM. Of the other two patients, the loss of nitrogen in one (G. W.) was slightly less and in the other slightly greater. It may here be noted that in general the degree to which the various patients complained of hunger corresponded roughly to the quantitative loss of nitrogen.

An excellent opportunity was afforded to study the functional relationship of the cholesterol content of the serum to the basal metabolic rate under the condition of a rapidly changing metabolic rate when this change was not due to the development of myxedema. On the basis of recent reports<sup>26</sup> a lowering of the basal metabolic rate when not due to the production of hypothyroidism might be expected to be followed by no change in the cholesterol content. The actual data may be noted in figure 2. It will be seen that there was a late decrease in the cholesterol content to an abnormally low level associated with a drop in the basal metabolic rate of 22 per cent. The metabolic rate had been at its low level for many days before the cholesterol content changed significantly.

A high level of the protein content of the serum has been reported in the presence of a low metabolic rate in myxedema.<sup>27</sup> This increase

26 Hurxthal, L. M. Blood Cholesterol and Thyroid Disease. III. Myxedema and Hypercholesteremia, *Arch. Int. Med.* **53**: 762 (May) 1934, Blood Cholesterol and Hypometabolism, *ibid.* **53**: 825 (June) 1934.

27 Decourt, J., Meyer, L., and Guillaumin, C. O. Sur le syndrome humoral du myxœdème, *Bull. et mém. Soc. méd. d'hôp. de Paris* **51**: 927, 1935.

TABLE 4—Data on the Loss of Weight, Intake and Output of Nitrogen and Output of Sodium Chloride\*

Patient	Sex	Standard Average Weight, Kg	Period, Days	Average Weight, Kg	Loss of Weight, Kg	Food, Calories per Day	Food, Calories per Kg	Protein Intake per Day, Gm	Protein Intake per Kg, Gm	Total Nitrogen Intake, Gm	Nitrogen Intake per Day, Gm	Total Nitrogen in Urine, Gm	Average Nitrogen in Urine per Day, Gm	Average Sodium Chloride in Urine per Day, Gm
F C	M	71	Preliminary	70.3	2.7	2,300	33	77.1	1.11	457.1	12.7	324.7	9.0	4.92
			36											
			I 9	67.0	4.1	356	5.3	32.0	0.48	45.1	5.0	64.3	7.1	3.83
			II 37	63.5	2.8	605	9.5	43.0	0.68	254.6	6.9	212.0	5.5	3.68
			III 10	62.1	0.0	800	13.0	57.0	0.92	91.2	9.1	65.3	6.5	5.23
L McM	F	70	Preliminary	55.8	2.6	1,100	20.0	39.0	0.69	98.9	6.2	65.7	4.1	3.59
			16											
			I 30	51.9	5.0	356	6.9	32.0	0.60	153.6	5.1	133.4	4.5	2.81
M W	M	66	Preliminary	65.0	0.8	1,700	25.0	97.0	1.49	130.3	10.9	119.5	9.9	7.18
			12											
			I 10	62.6	3.5	356	5.7	32.0	0.50	51.2	5.1	91.5	9.2	4.75
			II 9	60.3	1.1	598	9.9	34.0	0.56	49.0	5.4	60.8	6.8	2.40
			III 23	59.0	2.0	793	13.6	47.0	0.79	173.0	7.5	203.2	9.1	3.31
			IV 9	58.1	0.0	1,106	19.3	53.0	0.91	76.3	8.5	77.4	8.6	3.73

\* The values for the intake of food during the preliminary period are averages

was chiefly in the albumin fraction. It is therefore of interest to note (fig 4) that associated first with the lowering of the basal metabolic rate, yet without any evidence of myxedema, there was an increase in the globulin fraction, the albumin fraction remaining essentially unchanged. Later, however, the albumin fraction decreased, and there was a tendency toward a reversal of the albumin-globulin ratio. There was no albuminuria or evidence of a tendency to retention of fluid. The protein measurements returned to normal when the diet was later increased to 1,200 calories. In figure 4 it will be noted also that the calcium content of the blood, which varied between 9.6 and 10.2 mg

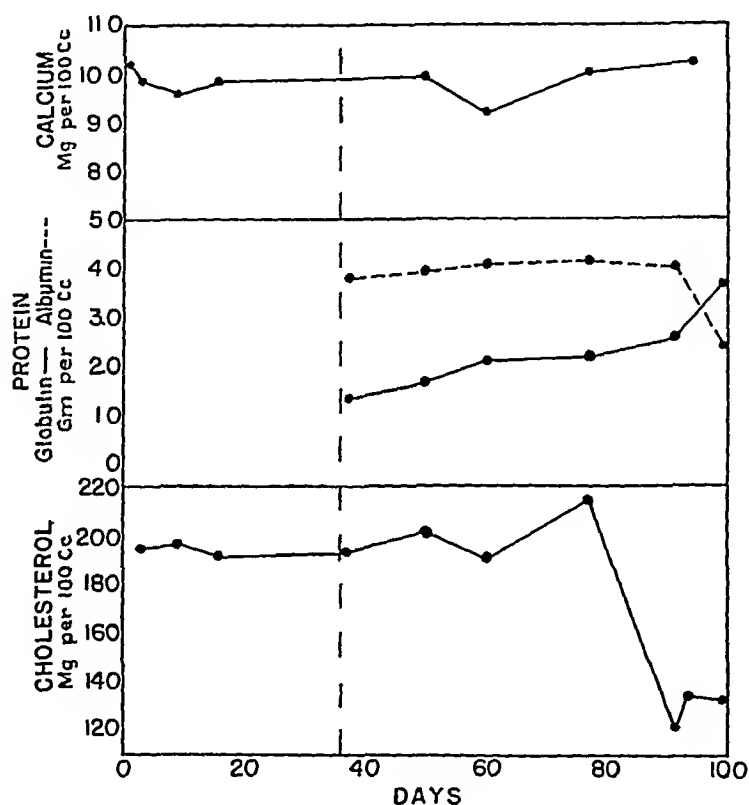


Fig 4—Graphs showing the effect of dietary restriction in patient F C on the serum cholesterol, blood calcium and serum albumin and globulin contents. The vertical line indicates the beginning of food restriction.

per hundred cubic centimeters on several occasions during the few weeks before dietary restriction was begun, showed no change as a result of the diet, although no calcium medication was given.

The blood sugar content during fasting was decreased (about 15 per cent), although the response to the ingestion of 100 Gm of dextrose was essentially unchanged.

The hemoglobin and erythrocyte content of the blood, despite the fact that the diet appeared to be deficient in iron, showed no significant changes.

## COMMENT

The state of heart failure in a given person is rarely a steady one, and since changes are constantly taking place, owing to many uncontrollable factors, it is extremely difficult to evaluate the effect of a specific procedure, particularly when this procedure involves a period of days or weeks. Since in our studies the patients were at complete rest in bed for many weeks, the question naturally arises as to what the effects of this prolonged rest alone might be. However, since the changes which we have described followed varying preliminary control periods of rest in bed and since these changes regularly began within a few days after dietary restriction was begun, it seems justifiable to attribute these changes to the dietary restriction. It is hoped that this question will be more positively answered from studies which are now in progress on the effects of less strenuous but long continued dietary restriction in ambulatory patients with heart disease.

The effects which we observed to be due to digitalis therapy in the presence of heart failure correspond to those reported by Stewart and Cohn<sup>22</sup>. Attributable to digitalis when given in the presence of heart failure are the following results: an increase in the output of the heart associated with a decrease in the arteriovenous oxygen difference, an increase in the stroke volume of the heart, a decrease in the cardiac rate, a decrease in the size of the heart, an increase in the vital capacity and diuresis. These changes occurred in the presence of both auricular fibrillation and normal sinus rhythm. Since these changes paralleled definite clinical improvement, there can be no doubt that they represented a return of the circulation toward a more efficient state.

Probably the most significant change indicating improvement is the decrease in size of the heart<sup>28</sup>. The procedure further produces benefit by decreasing the necessity of the heart for work. This is made manifest by the decrease in the output of the heart and in the consumption of oxygen as well as by the decrease in the arterial blood pressure. It is entirely possible that the improvement in the function of the heart muscle was the result simply of the decrease in the work of the heart. Yet there are so many other factors involved, such as chemical changes resulting from the reduction of the diet and possibly major fluctuations in the activity of many if not all the glands of internal secretion, that more direct effects on the functioning of the cardiovascular mechanism leading to improvement are not inconceivable.

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28 Harrison, T. R. The Pathogenesis of Congestive Heart Failure, *Medicine* 14 255, 1935

29 Footnote deleted by authors

One of the more striking effects of dietary restriction that we noted was a slowing of the heart rate. It was this feature which first attracted our attention to the possible value of such a procedure. Harrison, Ashman and Larson<sup>30</sup> have presented convincing evidence of the desirability of producing considerable slowing of the heart rate in the presence of myocardial hypertrophy. On the basis of comparative studies, they stated that they had come to believe that the slow heart rate in animals with thick cardiac fibers is advantageous because the recovery period of the heart is prolonged, i. e., it takes oxygen longer to diffuse through a thick fiber than through a thin fiber. Their evidence also indicated that heart failure may be due in part to a heart rate which is faster than optimal, and they stated in conclusion that their "data suggested further that if it were possible to reduce the cardiac rate to a level considerably below the normal, 'cardiac fatigue' would be much benefited." Wearn<sup>31</sup> likewise, in a demonstration of the relationship between fiber thickness and blood supply, reached the conclusion that, other things being equal, a thick muscle fiber is less adequately supplied with blood and hence oxygen than a thin muscle fiber. Since this supplying of blood is accomplished chiefly during diastole, it is obviously desirable in the presence of hypertrophy for the heart rate to be as slow as possible yet consistent with good cardiac function. The results just presented indicate clearly that a slowing of the heart rate beyond what is possible otherwise may be obtained with prolonged restriction of food.

There is reason to believe on the basis of our observations on patients with heart disease and those of Benedict and his associates on normal persons that in the presence of a normal heart rhythm the slowing of the heart rate which is obtainable by dietary restriction is more regularly observed and is of greater magnitude than that following digitalis therapy.<sup>32</sup> Of our six patients, only three showed a normal rhythm, one of these showed no signs of cardiac weakness (M. W.) and received no digitalis, whereas in another (G. W.) the slowing of the heart rate following digitalis therapy was not striking. That digi-

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30 Harrison, T. R., Ashman, R., and Larson, R. M. Congestive Heart Failure. XII. The Relation Between the Thickness of the Cardiac Muscle Fiber and the Optimum Rate of the Heart, *Arch. Int. Med.* **49** 151 (Jan.) 1932.

31 Wearn, Joseph T. The Circulation in Normal and Hypertrophied Hearts, *New England J. Med.* **212** 1238 (June 27) 1935.

32 (a) Robinson, G. C. The Therapeutic Use of Digitalis, Baltimore, Williams & Wilkins Company, 1923. (b) Mackenzie, J. New Methods of Studying Affections of the Heart. III. Action of Digitalis on the Human Heart, *Brit. M. J.* **1** 759, 1906. (c) Cohn, A. E. Clinical and Electrocardiographic Studies on the Action of Digitalis, *J. A. M. A.* **65** 1527 (Oct. 30) 1915. (d) Robinson, G. C. The Value of Large Single Doses of Digitalis in the Treatment of Heart Disease, *South. M. J.* **13** 396, 1920.



talis may slow the heart rate when the rhythm is normal is shown convincingly in figure 1. In the presence of auricular fibrillation dietary restriction appeared to have an effect in slowing the heart rate comparable to the effect that it has when the rhythm is normal.

It is of some interest to speculate as to the mechanism involved in this slowing of the heart rate. We are inclined to attribute it to diminished sympathetic activities associated with a depression of the functional activity of the adrenal gland. The general state brought about by prolonged dietary restriction appears to be one of universal depression of activity of the endocrine glands, possibly through a diminution in the activity of the anterior lobe of the pituitary gland, hence, such effects as a diminished blood pressure, slower pulse rate, decreased metabolic rate, diminution in sexual desire in men<sup>1</sup> and cessation of the menses in women<sup>33</sup>.

One of the most striking and clearcut evidences of clinical improvement which we observed was in regard to the respiratory exchange and vital capacity. Peabody, Wentworth and Barker<sup>34</sup> and Peabody and Wentworth<sup>35</sup> were the first to point out that an increase of the minute volume of the lungs and a decrease in the vital capacity occurred as heart failure became more pronounced. These studies were later amplified by Harrison, Turley, Jones and Calhoun,<sup>36</sup> who also observed that in patients with congestive heart failure the degree of dyspnea (and hence the extent of weakness of the left ventricle) was proportional to the expression  $\frac{\text{ventilation}}{\text{vital capacity}}$ , ventilation referring to the respiratory minute volume. Since in our patients the pulmonary ventilation decreased considerably while the vital capacity became significantly greater, the beneficial effect is apparent. The increase in vital capacity alone represents, under the circumstances, positive evidence of an increase in cardiac strength, for the comprehensive researches along this line by Peabody and his associates (1915 to 1922), amply confirmed, have demonstrated that the measure of the vital capacity of the lungs represents perhaps the most important single easily measurable guide of cardiac strength.

33 (a) Kurtz, C. Alimentare Amenorrhoe, Monatschr f Geburtsh u Gynak **52** 367, 1920. (b) Dietrich, H. A. Kriegsamorrhoe, Zentralbl f Gynak **41** 157, 1917.

34 Peabody, F. W., Wentworth, J. A., and Barker, B. I. Clinical Studies of the Respiration. V. The Basal Metabolism and the Minute-Volume of the Respiration of Patients with Cardiac Disease, Arch Int Med **20** 468 (Sept.) 1917.

35 Peabody, F. W., and Wentworth, J. A. Clinical Studies of the Respiration. IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch Int Med **20** 443 (Sept.) 1917.

36 Harrison, T. R., Turley, F. C., Jones, E., and Calhoun, J. A. Congestive Heart Failure. X. The Measurement of Ventilation as a Test of Cardiac Function, Arch Int Med **48** 377 (Sept.) 1931.

The most extensive and detailed studies on the effect of prolonged dietary restriction on human beings are those of Benedict and his associates. Their report might have led us to anticipate many of the observations which we made and which we have reported here. In most respects in which similar factors were studied (blood pressure, heart rate, oxygen consumption) our data agreed with theirs, although they dealt with young, healthy persons not confined to bed, whereas our studies concerned older persons with heart disease who were kept in bed. There was surprisingly little variance in the effects observed. Thus, in the six patients whom we studied the decrease in oxygen consumption averaged 18 per cent, whereas in the Y M C A students (squad A) the average decrease in oxygen consumption with a corresponding loss of weight was 19 per cent<sup>1</sup>. Evidently the metabolism tends to respond to influences such as dietary restriction no more in younger persons than in older persons.

One important difference, however, in response in these two groups was in respect to the level of water exchange, as measured by the intake of fluid and the output of urine. We purposely permitted our patients to drink as much water as they desired, in order to observe the spontaneous change which might occur in the level of water exchange. A considerable decrease in the intake of fluid (and hence in the output of urine), such as Benedict and his associates observed in the Y M C A students, appears to be desirable in patients with heart disease. In only one of our patients, however, was there a diminution in the level of water exchange to a significant degree.

Keeton and Bone,<sup>37</sup> in describing their data on the metabolic effects of the reduction of weight in obese persons, indicated that these effects are not comparable to those observed when the reduction in weight takes place from a normal to an underweight level, i. e., the decrease in the level of oxygen consumption and loss of weight in an obese person is only proportional to and not greater than the percentage decrease in surface area. This is in agreement with the results which we observed in one obese patient (C M) whose weight was reduced to a normal level. We may therefore be led to expect a greater physiologic effect on the cardiovascular state, in the presence of heart disease, from a reduction of weight in a patient of normal size than from a reduction of weight in an obese patient. It is self-evident that a fat patient with cardiac weakness should reduce his weight. There may be some hesitancy on the part of the physician, on the other hand, to recommend a reduction in the weight of a patient of normal or low weight. Yet on

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<sup>37</sup> Keeton, R. W., and Bone, D. D. Diets Low in Calories Containing Varying Amounts of Protein. Their Effect on Loss of Weight and on the Metabolic Rate in Obese Patients, *Arch. Int. Med.* **55** 262 (Feb.) 1935.

the basis of our data it appears to be even more desirable that a patient of normal weight with heart disease should reduce his weight

#### SUMMARY

Six patients were studied, all save one of whom showed signs of severe congestive heart failure. Observations were made on arterial and venous blood pressure, cardiac rate, velocity of blood flow, cardiac output, respiratory rate, pulmonary ventilation, oxygen consumption, basal metabolic rate, vital capacity, response to exercise, muscle strength, output of urine, intake of fluid, intake and output of nitrogen, output of sodium chloride, red blood cell count, hemoglobin content and blood sugar level. In addition, in the case of one patient repeated measurements were made of the serum protein, cholesterol and calcium contents of the blood. In this case also electrocardiograms and roentgenograms were repeatedly made.

An attempt was made to separate as much as possible the effects of rest in bed and sedatives, digitalis therapy and dietary restriction.

The dietary restriction was such as to effect a loss of weight of approximately 10 per cent over two or three weeks. Restriction was begun with a diet which had a caloric content equivalent to that of the Karel diet. With one exception the weight was reduced from a normal or slightly undernormal level. The one exception was the case in which the weight of an overweight patient was brought to an average level.

The effects attributable to digitalis were slowing of the heart rate, increase in the vital capacity, decrease in the respiratory rate and the respiratory minute volume, increase in the cardiac output with a decrease in the arteriovenous oxygen difference, diuresis and decrease in the size of the heart.

The effects on the cardiovascular and respiratory systems attributable to dietary restriction were further slowing of the heart rate in the presence either of sinus rhythm or of auricular fibrillation, a decrease in the systolic and the diastolic blood pressure even from a normal level, slight or no increase in the velocity of the blood flow, an increase in the vital capacity and a decrease in the respiratory rate and the respiratory minute volume, in the oxygen consumption and the basal metabolic rate, in the cardiac output with slight or no decrease in the arteriovenous oxygen difference, in the venous pressure, in the cardiac work and in the size of the heart. These were changes at rest. There was corresponding evidence of improvement during exercise.

There was a decrease in the level of the blood sugar during fasting, though the tolerance curve was practically unchanged. The hemoglobin content of the blood and the erythrocyte count were unchanged.

In one patient the serum cholesterol content decreased to an abnormally low level after the basal metabolic rate had been at a low level for a few weeks. In this patient also there was first an increase in the globulin fraction of the serum protein with later a decrease in the albumin fraction. There was no change in the calcium content of the blood.

There was evidence of a negative nitrogen balance during the period of extreme dietary restriction (356 calories). There was no relationship between the quantity of nitrogen lost and the magnitude of the changes observed.

There was regularly a decrease in the output of sodium chloride following dietary restriction. In only one patient was the level of fluid exchange (intake of fluid and output of urine) considerably diminished. The intake of fluid and sodium chloride was unrestricted.

In four of the patients considerable clinical improvement was attributed to the dietary restriction, in one the improvement was moderate. This was the patient whose weight was reduced from an overweight level to an average level. In the other patient no significant clinical improvement was observed after the dietary restriction.

# Progress in Internal Medicine

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## GASTRO-ENTEROLOGY IN 1935

GARNETT CHENEY, M D

SAN FRANCISCO

In reviewing the literature on gastro-enterology for 1935 the same policy has been followed as last year. Many original articles have been written on many subjects, but only certain fertile fields have been touched on in this review, and the barren ones have been ignored. Two subjects dealing with peptic ulcer—the treatment of massive hemorrhage and the inadvisability of gastro-enterostomy for uncomplicated duodenal ulcer—have received particular attention. Gastrosopy and gastritis and the recently developed methods of medical treatment for peptic ulcer have not been discussed this year, as it is as yet too soon to draw any mature conclusions about these topics, which were covered in 1934.

### ESOPHAGUS

With an improved technic for the roentgen examination of the esophagus and with the wider use of esophagoscopy, more and more clinical attention is being paid to the occurrence of peptic ulcer of the esophagus. Roessler<sup>1</sup> in an excellent review of this subject has tabulated the detailed observations on 72 cases reported in the literature and has added 5 case reports of his own. He has left out the reports of 79 other cases because of insufficient data. In 88 per cent of all the cases of ulcer the lesion was located within the lower 4 cm. of the esophagus, the majority being in the anterior wall. As islands of gastric mucosa are more frequent in the upper part of the esophagus, their presence is not directly responsible for the lesion. A primary disturbance in the function of the vegetative nervous system with a secondary spastic condition and cardiospasm is of greater importance. Vascular spasm with its resulting interference with nutrition is a predisposing factor. Regurgitation of acid stomach contents through the cardiac orifice is of only secondary importance, as it occurs in a variety of conditions without the formation of ulceration.

Esophageal ulcer and its complications may occur without any symptoms at all, just as do peptic lesions elsewhere. As a rule the complaints and the site of pain give sufficient indication of the presence

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<sup>1</sup> Roessler, W. Ueber das Ulcus pepticum oesophagi, Deutsche Ztschr f Chir **245** 333, 1935

of the ulcer to make its localization possible. Pain is the outstanding symptom. It follows eating and even swallowing and is constantly located in the midline, high up in the epigastrium and often under the lower portion of the sternum. Hemorrhage was noted as a symptom in a little over half the cases and was fatal in 14 instances. Functional obstruction and organic obstruction with vomiting are not uncommon, and esophagoscopy with tissue biopsy may be essential to differentiate a peptic lesion from cancer. An ulcer crater may be visualized roentgenographically. Roessler<sup>1</sup> has demonstrated this important diagnostic point with excellent roentgenograms.

The prognosis is not a happy one. The complications of hemorrhage and obstruction often prove fatal. If the ulcer heals, some degree of obstruction follows, owing to the accompanying scarring. Marked improvement in the symptoms occurs, but the patient has them year in and year out. Operative treatment is to be avoided unless obstruction demands it. Esophagogastrostomy has given good results.

Acute ulcerative esophagitis is rarely recognized during life. Bartels,<sup>2</sup> in examining 6,000 autopsy specimens, encountered 82 instances of this condition, an incidence of only 0.013 per cent. He presents a detailed analysis of the pathologic and clinical data and attempts to correlate them. He concludes from the clinical standpoint that esophagitis should be recognized from the symptoms and signs it produces. It commonly occurs in the debilitated but not necessarily dying patient. The inflammation is well localized in the lower third of the esophagus, and it must be accepted that the regurgitation of acid gastric juice into this region is a contributing cause. Vomiting is a common symptom in these cases of acute ulceration and acts as an important factor in permitting the gastric contents to come in contact with the wall of the esophagus. So-called peptic ulcer of the esophagus was not encountered in this entire series of cases.

Since Torek first successfully removed the thoracic portion of the esophagus for carcinoma in 1913 and the patient survived thirteen years, dying of pneumonia, surgeons have hoped to repeat this triumph. Little progress has been made, however, particularly as the operation carries with it a mortality of almost 100 per cent. Consequently, Moersch's<sup>3</sup> description of the successful removal of a carcinoma of the esophagus by surgical diathermy is of special interest. Esophagoscopy examination of his patient revealed a pedunculated tumor the size of a walnut at the junction of the upper and middle thirds of the esophagus, which was destroyed by diathermy. Six months later the patient was perfectly

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<sup>2</sup> Bartels, E. C. Acute Ulcerative Esophagitis, *Arch. Path.* **20** 369 (Sept.) 1935.

<sup>3</sup> Moersch, H. J. Carcinoma of the Esophagus Removed by Surgical Diathermy, *Proc. Staff Meet., Mayo Clin.* **10** 433, 1935.

well and could eat anything without the least difficulty. He had gained 20 pounds (9 Kg) in weight. This is apparently the first successful operation of its kind to be reported.

#### STOMACH

As reports of cascade stomach are meager in the English literature, Upham<sup>4</sup> has reviewed this picturesquely named condition and has outlined the criteria on which a diagnosis may be justified. Cascade stomach, or "shelf stomach," is not to be considered a variety of hour-glass stomach, it is the result of a special change in the form and in the position of the stomach. In both conditions this organ is divided into two parts, but here the similarity ends. In a case of hour-glass stomach, as the term implies, the upper and the lower pocket are of approximately the same size, and one is almost directly above the other. Also the tonicity in these two conditions is the same. In a case of cascade stomach there is dilatation of the upper pocket, which is enlarged posteriorly, and the walls are flaccid. The fluid contents of this large toneless sac in the upper posterior portion of the abdomen splash over into the smaller, more anterior, pocket if the position of the patient is suddenly changed.

Various causes for this phenomenon have been described. In some cases it is anatomic, due to obstruction in the midportion of the stomach, as from a callous ulcer. Great pressure then occurs in the upper sac, displacing the left crus of the diaphragm and other structures which normally occupy the left upper quadrant of the abdomen. In the transitory forms it is spasm of the oblique muscles drawing the stomach up which has been described as the "cup and spill" type. Extreme gaseous pressure or tumor in the splenic flexure of the colon may produce the deformity. It has been said also that it is due to increased gastric pressure from aerophagia. Upham's conception of the cause differs somewhat. The first step is a changed position of the spleen—a lateral displacement, permitting an abnormal mobility of the fornix. This increase in space leads to the second factor, namely, the stomach prolapses posteriorly, rotating on the splenic artery and the tail of the pancreas, causing the damming behind which the cup forms and causing fluid to cascade into the lower pocket. Pressure necrosis of the surrounding fat may exaggerate the abnormal position and increase the obstruction.

Such a conception explains the physical factors by which cascade stomach is acquired, and when pathologic changes are present within the stomach they give rise to a perverted motor function which produces

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4 Upham, R. Cascade Stomach. A Review, *Am J Digest Dis & Nutrition* 2 38, 1935

the same condition. A typical case is mentioned in which operation was performed. The phrenicogastric ligament was absent, and the spleen was not fixed. The only support of the stomach was at the cardia, allowing it to fall into a lower position than normally and thereby producing the "champagne cup" deformity.

The common symptoms are distention, aerophagy and belching, but the characteristic feature is that the patient is ordinarily completely relieved by lying on the left side, which usually permits the upper pocket to empty. On physical examination there may be prominence of the left side in the region of the eighth, ninth and tenth ribs and in the hypochondrium. The absolute diagnosis depends on the roentgen examination, and the stomach should be examined as a routine with the patient in the left lateral position, as the two pockets may in some measure overlap each other. Medically, there is little of value in the form of treatment, and surgical intervention has rarely brought relief except when intrinsic pathologic changes were present. Antispasmodics may be of value when the deformity is reflex from some other condition.

Seale Harris,<sup>5</sup> of Birmingham, Ala., has written a fascinating report on the gastro-intestinal manifestations of hyperinsulinism. Every physician who reads the present review of gastro-enterology should read Harris' report in the original, as it contains many case histories taken both from the American and from the foreign literature as well as from the author's extensive experience. These are of particular value and of intense interest because the manifestations are so protean in character that they are better appreciated by a careful perusal of a large number of case histories than by any more or less stereotyped textbook form of discussion.

Gastro-enterologists must become "hyperinsulinism conscious," as in most cases the patient connects his symptoms with the stomach. Not only may he have the milder type of gastro-intestinal complaints, but not infrequently he may complain of severe abdominal pains. Several patients have been operated on under a mistaken diagnosis of peptic ulcer, appendicitis or disease of the gallbladder, and hyperinsulinism has been reported coincident with these same disorders as well as with pancreatitis. Although distressing hunger coming on a number of hours after meals and relieved by the taking of food is characteristic, it has frequently led to a false diagnosis of duodenal ulcer. Actually in the cases in which the symptoms are more severe hunger may not be a symptom, and there may be a real disgust for food, amounting sometimes to sitophobia.

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<sup>5</sup> Harris, S. Gastro-Intestinal Manifestations of Hyperinsulinism, *Tr Am Gastro-Enterol A*, 1935, p 31



It is again emphasized that while determinations of blood sugar in the fasting state may reveal low values, the results are often normal, and hypoglycemia may be manifest only after a four to six hour dextrose tolerance test. Glycosuria may be found at certain periods, particularly in obese patients, and some may be considered potential diabetic subjects. All low blood sugar values may not be due to hyperinsulinism, as disease of the liver or of certain endocrine glands may lead to hypoglycemia. Studies of the blood sugar content should be carried out in many cases of "nervous indigestion," as a disturbance in sugar metabolism may be an underlying factor in some cases. A carefully planned dietary regimen, usually with a low amount of carbohydrate and high content of fats, often relieves the patient who is suffering from hyperinsulinism.

*Gastric Physiology and Secretion*—Oil of peppermint has long held an esteemed position as a household remedy for the treatment of gastric pains and distress. Its use was mentioned during the time of Charlemagne. On account of its popularity Meyer, Scheman and Necheles<sup>6</sup> have studied its action on the secretion and motility of the stomach, utilizing both dogs and human beings. Previous observers have reported that peppermint increases the amplitude and vigor of the contractions of the stomach but has no influence on the secretion of hydrochloric acid. It is stated also that relief from gastric distress is due to an anesthetic action and that oil of peppermint has a cholagogue action. Eating peppermint candy relieves the pain caused by hunger and the distress after a heavy meal.

The authors found that oil of peppermint inhibited the secretion of acid by the resting stomach and greatly reduced its flow after the administration of an alcohol test meal and stimulation with histamine. Most of the 17 patients with peptic ulcer showed depressed or no acidity after the administration of alcohol and oil of peppermint as compared with that after the administration of alcohol alone. Substitution of olive oil failed to produce this change. Study by the balloon method showed that the gastric motility was not depressed by peppermint in physiologic doses. Similar studies by means of roentgenograms revealed a decrease in the emptying time.

As oil of peppermint is a mixture of a number of substances, further tests with its various components will be necessary. The menthol which it contains has no acid depressing effect. A number of patients with peptic ulcer are now under treatment with essence of peppermint, but no conclusions can as yet be drawn, although a few are definitely relieved of pain. If the pain of ulcer is due to local ischemia and

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6 Meyer, J, Scheman, L, and Necheles, H. Action of Oil of Peppermint on the Secretion and Motility of the Stomach in Man, Arch Int Med 56 88 (July) 1935

asphyxia, this essential oil might produce local hyperemia and give relief. This problem is being pursued further.

In considering the rationale of commercial mucin in the treatment of peptic ulcer Baltzer<sup>7</sup> has pointed out that watery mucous soups are superior to mucin preparations as they do not stimulate gastric secretion by their protein content and they do tend to neutralize free acidity. The alleged protective action of ingested mucin does not take place, as the mucin is mixed with the gastric contents. The normal secretion of gastric mucus acts as a barrier between the wall of the stomach and the contents, and medication by mouth cannot duplicate this function.

As achlorhydria is often thought to be a precursor of cancer of the stomach and of anemia, particularly of the Addisonian type, Bloomfield and Polland<sup>8</sup> have made a follow-up report of 45 patients with an unexplained anacidity to histamine. Originally these patients had no gastro-intestinal symptoms of importance, and the absence of free gastric acidity was an incidental finding. From one to seven years later none of them had malignant disease of the stomach or anemia in any form. There was a return of free hydrochloric acid in only 1 of 25 cases.

The late Dr. Eugene Klein, of New York, made extensive studies of gastric secretion. His paper<sup>9</sup> dealing with achlorhydria following partial gastrectomy for ulcer is based partly on clinical observations and partly on experimental observations on dogs. His findings are of particular importance in stressing that the effects of an operation on the stomach should be considered primarily from the point of view of altered function rather than of altered anatomy. Removal of the antrum of the stomach produces achlorhydria in only a certain proportion of cases, because only the secondary or chemical phase of gastric secretion is eliminated and the primary reflex phase through the vagus system, the phase of late intestinal stimulation and the less clearly defined phase of spontaneous secretion apparently dependent on conditioned reflexes remain unaltered. It can readily be shown by studies of the secretion in the transplanted gastric pouch of the dog followed by partial gastrectomy that food fails to produce a secretion of free hydrochloric acid. This achlorhydria is due not to a loss of acid cells, as they are situated in the body and in the fundus of the stomach, but to the loss of the antrum, through which the chemical stimuli of the food (secretagogues) act. However, a small dose of histamine which acts directly on the glandular cells stimulates a normal secretion of

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7 Baltzer, F. Der Magenschleim, *Arch f. Verdauungskr.* **58** 33, 1935.

8 Bloomfield, A. L., and Polland, W. S. The Fate of People with Unexplained Gastric Anacidity, *J. Clin. Investigation* **14** 321, 1935.

9 Klein, E. Gastric Secretion. V. Achlorhydria Following Partial Gastrectomy for Ulcer, Studies with Histamine and the Transplanted Gastric Pouch. *Arch. Surg.* **30** 162 (Jan.) 1935.

hydrochloric acid In other words, partial gastrectomy does not destroy the ability of the stomach to produce free acid but only interrupts the natural train of events for the secondary phase of the secretion of hydrochloric acid

Clinically the amount of acid present in the test meal after operation will depend on the following factors (1) the amount of secretory stimulation which persists which is chiefly vagal and reflex, (2) the relative percentage of secretion which before operation is due to the secondary phase, (3) the amount of neutralizing substances contained in regurgitated duodenal contents, and (4) any changes which may occur in the acid-secreting cells themselves It is evident then that anacidity will be the result of gastrectomy only when a large proportion of the gastric secretion occurs in the secondary phase, when the primary or vagal phase is not profuse and when a large amount of duodenal regurgitation occurs which can neutralize any small amount of acidity present When these conditions are reversed acidity will persist After an operation for duodenal ulcer, acidity is more likely to persist than after an operation for gastric ulcer, because of removal of the first part of the duodenum, which exerts impulses inhibitory to gastric secretion Section of the left, or anterior, vagus nerve, if added to the operation of gastrectomy, thereby reducing the primary vagal phase, is usually sufficient to produce achlorhydria

It should be clearly recognized that after gastrectomy the use of histamine as a stimulant to acid secretion instead of a test meal is not comparable to normal physiologic processes It is a powerful chemical stimulus acting directly on the cells After its use all but 4 of Klein's 17 patients showed free hydrochloric acid All these patients showed anacidity to the gruel test meal, which is probably more in line with the conditions under which a patient lives The use of histamine after partial gastrectomy supplies a stimulus similar to the one which has been removed, and it is really surprising that any subject shows anacidity after its use, as the acid cells are still present More attention should be focused on the separate phases of gastric secretion in both normal and pathologic conditions

Occasionally, a case of complicated peptic ulcer is encountered in which surgical treatment is not indicated One aim of therapy must be to reduce the acid secretion of the stomach to a minimum Jejunal feeding by stomach tube or even by jejunostomy is recommended, as it is said to lower the acidity of the gastric contents Appell<sup>10</sup> has tested the validity of this statement by determining the effect of jejunal feeding on gastric acidity and secretion in dogs He found that any food placed in the jejunum stimulated gastric secretion but that some foods produced greater gastric acidity than others The degree of

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<sup>10</sup> Appell, A A Effect of Jejunal Feeding on Gastric Acidity, *Arch Surg* 30 875 (May) 1935

acidity was about equal in jejunal and in oral feeding when the dogs were fed three times a day, but when they were fed five times a day acidity was actually higher when food was introduced into the jejunum. From the author's experimental findings it appears that the beneficial results of jejunal feedings reported in certain cases of peptic ulcer were not due to a lowering of the gastric acidity.

A new method of directly observing the development of experimentally produced peptic ulcer in dogs has been described by Harper,<sup>11</sup> of the Mayo Clinic. The ulcers were produced in a loop of intestine forming a fistula from an isolated gastric pouch to the abdominal wall and occurred in each animal operated on. The chemical action of the gastric secretion was found to be of prime importance in initiating and maintaining the lesion, and the increasing vulnerability of the intestinal mucosa the farther it was from the stomach was also demonstrated. An ulcer in an isolated pouch caused loss of appetite, vomiting and loss of weight, just as an ulcer in the main portion of the gastrointestinal tract may cause the same symptoms. Of particular therapeutic interest was the fact that in 5 dogs the development of ulceration was prevented by the introduction into the pouch twice daily of a protective emulsion of gelatin, acacia, olive oil and lecithin and that healing of an already existing ulcer could be accomplished in three weeks by the same procedure.

Rafsky<sup>12</sup> has studied the crystalline elements observed following gastric lavage and their relation to disease of the gallbladder. Photomicrographs of the crystals observed in the gastric contents are compared with crystals observed in the bile and in the stones obtained at the time of surgical exploration. He examined 91 patients—58 per cent came to operation and 22 per cent comprised a normal control group. Crystalline elements were noted preoperatively in appreciable amounts in 87 per cent of the patients operated on and were similar to the crystals in the bile and in the stones removed at operation. These elements were present in less than half the patients in the control group and then only in small amounts. When gastric lavage revealed many cholesterol crystals, together with an abundance of calcium bilirubinate pigment, cholelithiasis was present in 97 per cent of the patients. Three case reports are presented to illustrate the importance of the microscopic examination of lavage washings for crystalline elements in cases in which disease of the gallbladder is suspected.

*Peptic Ulcer*—Many articles appear every year on the etiology of peptic ulcer, and most of them add nothing to one's knowledge of this

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11 Harper, F. R. Development and Treatment of Peptic Ulcer. An Experimental Study, *Arch Surg* **30** 394 (March) 1935.

12 Rafsky, H. A. Stomach Lavage Microscopy as an Aid in the Diagnosis of Biliary Tract Disease, *Am J Digest Dis & Nutrition* **2** 214, 1935.

disorder While Robinson's<sup>13</sup> paper on this subject adds nothing startlingly new, his conception of the relationship of constitutional factors as the underlying cause of this common ailment places this disorder in a somewhat different clinical category from that which is commonly accepted His analysis is based on observations of 70 patients with peptic ulcer

His factual information supports the neurogenic theory of "peptic" ulceration Fear, anxiety and apprehension stimulate the vegetative nervous system to the stomach and duodenum, resulting in hypermotility, hyperchlorhydria and vascular spasm This spasm leads to thrombosis, ischemia, necrosis and ulceration Factors such as hyperacidity, focal infection and diet *have absolutely nothing to do* with the etiology of the disease The racial selectivity of peptic ulcer supports this theory Peptic ulceration does not occur in lower animals and is rare in the Negro and lesser pigmented races It is rarely found in members of the Caucasian race under primitive conditions There is a definite type of so-called ulcer build and personality, which the author describes in convincing detail and which has been generally recognized by the medical profession but only as an impression The results of physical measurements and character studies show that the "typical ulcer type" of patient is a long, lanky, hyperkinetic person, usually a male, who is probably underweight and who has considerable dynamic energy Only in a few subjects is it difficult to elicit a history of considerable nervous unrest

As opposed to ulceration elsewhere in the gastro-intestinal tract, it is emphasized that peptic lesions are localized in a small ulcer-bearing area In over 95 per cent of the cases of ulcer of the stomach the lesions are bunched together within 2 inches (5 cm) of the incisura The few ulcers which occur well outside this area have a different etiology and present a different clinical picture This limited ulcer-bearing area must be accounted for by some difference in its physiology or structure from that of the surrounding tissues Anatomically it is this region that has the richest vegetative nerve supply Pathologic studies reveal that the greatest amount of damage in cases of peptic ulcer is produced beneath the mucosa and that thrombosis is probably responsible for the induration and thickening of the serosa and subserosa Vascular spasm and thrombosis produce a destructive process which is dry and clean, and this is precisely what is observed in a peptic ulcer It is clear that the ischemic condition of the submucosal structures cannot be due to hydrochloric acid or pepsin, it is due to a rain of nervous stimuli acting on a small portion of the gastro-intestinal

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13 Robinson, S C On the Etiology of Peptic Ulcer An Analysis of Seventy Ulcer Patients, *Am J Digest Dis & Nutrition* 2 333, 1935

tract which produces hypertonicity of the vascular bed leading to spasm. Such stimuli are of psychogenic origin and produce hypermotility, hypersecretion and hyperchlorhydria.

Andersen's<sup>14</sup> study of pyloric gastritis in Denmark led him to the belief that this is not a disease entity and that gastroduodenitis not only embraces this condition but is intimately related to the development of peptic ulceration. The pyloric syndrome of recurrent periodic gastric pain relieved by food, hypersecretion, delayed emptying of the stomach, hematemesis, melena and occult blood in the stool is not pathognomonic of chronic ulcer but may be noted in the absence of ulcer when only gastritis is present. Andersen was able to collect reports of 21 cases in which the pyloric syndrome was noted and in which operation was performed and no ulceration was observed. Histologic study of the resected portion of the wall of the stomach revealed pyloric gastritis. These patients had all the classic symptoms of ulcer, and 7 had had manifest bleeding. Andersen then studied 160 patients with peptic ulcer who were hospitalized. They were divided into three subgroups. The first was composed of 88 patients with definite roentgenographic signs of ulcer, the second, of 59 patients without definite signs of ulcer, and the third, of 13 patients who had not been studied roentgenographically. The symptoms in the first two groups were essentially the same. The "pyloric syndrome" occurred more frequently in patients without roentgen signs of ulcer, contrary to the general belief that it is characteristic of peptic ulceration. It was present in 90 per cent of the patients who did not show roentgen signs of ulcer and in only 78 per cent of those who showed positive signs. These findings emphasize the fact that inflammation and not ulceration is the underlying cause of the symptomatology. The late appearance of pain after eating is due to the increased movement of the inflamed gastric wall after the stomach empties.

Recurrent vomiting was a frequent symptom of gastroduodenitis uncomplicated by organic obstruction. Hyperacidity and hypersecretion were as common in the cases of gastroduodenitis without ulceration as in cases of peptic lesions. Six hour gastric retention occurred in the patients who were free from ulceration just as well as in those with ulceration and is in no way helpful as to the differential diagnosis. Six hour retention as a disturbance in motor function also was observed in patients without gastroduodenitis and is not to be used as a criterion of organic disease of the pyloric region. Twelve hour retention is considered of far greater diagnostic significance. As regards bleeding, severe hemorrhage with hematemesis and melena is common in patients with gastroduodenitis without ulceration, but in patients with no history of loss of blood the demonstration of occult blood in the stools is

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14 Andersen, T. Ueber Gastroduodenitis. *Acta med. Scandinav.* **84** 185, 1935.

uncommon. In other words, the patient bleeds acutely and profusely as a rule, and there is no chronic oozing of blood. When ulceration or a neoplasm is present oozing is common.

Roentgen examination may definitely determine whether a peptic ulcer is present. However, only the demonstration of the niche is to be accepted as a positive indication of its presence. Indirect evidence and "typical deformity" are not evidence of ulceration and may be encountered in cases of gastroduodenitis alone. Studies of the gastric mucous membrane demonstrated pathologic rugae in all but 4 cases of gastroduodenitis, and similar changes were noted only twice in 77 control cases. The author concludes that the roentgenologist should attempt to diagnose only gastroduodenitis with or without demonstrable ulceration and that the diagnosis of the complicating peptic ulcer should be added only when visualization of the niche is possible.

As peptic ulcer involving the greater curvature of the stomach is uncommon, Matthews<sup>15</sup> has reviewed the literature and has reported on 2 cases of his own. Although reports of 139 cases of ulcer of the greater curvature were found, only 22 cases were described carefully enough to make certain the demonstration of the lesion. Preoperatively in both the author's cases the condition had been thought to be malignant.

It has frequently been stated that peptic ulcer is uncommon in the presence of diabetes mellitus. If this is so, it will be of particular interest because diabetic subjects are notoriously liable to many complications and because vascular changes with thrombosis, which many think the underlying cause of peptic ulcer, are unusually common in diabetes. A. J. Leser<sup>16</sup> has attacked this problem from a statistical point of view. He analyzed the incidence of diabetic patients and of patients with ulcer in a large Viennese clinic over a ten year period. Only 2 of the 119 diabetic patients treated with insulin had peptic ulcer. Both patients were males. Leser found the incidence of peptic ulcer in over a thousand nondiabetic males to be 5.22 per cent, and in 283 females, 1.87 per cent. Autopsy revealed in almost 1,000 nondiabetic subjects that ulcer was present in 20.5 per cent of the males and in 18.5 per cent of the females. In the group of 34 diabetic subjects who came to autopsy, no ulcer was found in a male and only 1 in a female, making an incidence of 0 per cent in males and 4.17 per cent in females. It is apparent then on both clinical and pathologic grounds that peptic ulcer is relatively rare in diabetic subjects but that there is at present no satisfactory explanation of this fact.

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15 Matthews, W. B. Peptic Ulcers Involving the Greater Curvature of the Stomach, *Ann Surg* **101** 844, 1935.

16 Leser, A. J. Ueber das peptische Magen-und Zwölffingerdarmgeschwür und Diabetes, *Arch f klin Chir* **182** 143, 1935.

The management of severe hemorrhage complicating peptic ulcer of the stomach and duodenum has received a great deal of attention recently. Some of the authoritative articles dealing with such important points as diet, starvation, nutritive intravenous injections, transfusions and surgical treatment differ so widely and positively in their statements of what should and should not be done that they are well worth reviewing as a group. One can conclude only that no standardized form of treatment is the only one that can be successful in all cases and that in certain serious conditions thoughtful consideration of the individual problem presented is necessary before an attempt is made to outline the therapy required.

Tage Christiansen<sup>17</sup> studied 289 cases of massive hemorrhage due to peptic ulcer which were reported during the ten years prior to 1934 in the city hospital of Copenhagen. In presenting a review of the literature on this subject he noted that the mortality in most countries is slightly greater than 10 per cent but that in Scandinavia it is slightly less. The mortality in his series was only 7.9 per cent, with a higher percentage for women than for men. The outlook was far better among patients in whom hemorrhage was the first and only symptom of peptic ulcer, and there was practically no difference in the mortality in cases of short duration and in those of long standing. In the last five years the mortality was almost twice that of the previous five years, despite the much wider use of blood transfusion in treating these patients. Eight of 13 patients who had recently been given transfusions died, and the author not only believes that transfusions have not reduced the number of deaths from massive hemorrhage but even suggests that they may have contributed to its increase. The hemoglobin determination was an important factor in the prognosis. When it was below 60 per cent the death rate was almost four times that when it was above 60 per cent.

Autopsy was performed in 16 of the 23 fatal cases. As 1 (12 cases) or more ulcers were found in each case, diffuse bleeding of the gastric mucosa (gastrostaxis) as a cause of fatal hemorrhage did not occur in this group of patients.

De la Viesca<sup>18</sup> has analyzed 177 cases of copious hemorrhage from the stomach noted at the university clinic in Leipzig over the five year period from 1929 to 1934. In 130 patients, or 73.5 per cent, the bleeding was due to gastroduodenal ulcer, in 24, or 13.6 per cent, to carcinoma, and in 18, or 10.2 per cent, to gastritis. In the few remaining patients it was due to miscellaneous causes.

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17 Christiansen, T. On Massive Hemorrhage in Peptic Ulcer, *Acta med Scandinav* **84** 374, 1935.

18 de la Viesca, P. Die grosse Magenblutung, *Arch f Verdauungskr* **58** 22, 1935.



Heavy bleeding was more common from ulcer of the stomach (19.5 per cent) than from ulcer of the duodenum (7.2 per cent). Observations of the degree of anemia and of the blood pressure were the best guide as to the course of the hemorrhage. The greater number of the patients showed fever, which usually subsided quickly. Ninety per cent of the patients with ulcer had hyperacidity. Repeated hemorrhages occurred in 8.4 per cent, and 27.2 per cent of these patients died. Tests of the stools for occult blood indicated that the bleeding lasted as a rule for from two to three weeks. In 6.6 per cent of these cases of bleeding ulcer death occurred. Over twice as many males as females succumbed. The patients over 40 years old were more liable to death than the younger patients (a ratio of 8:1). As mortality statistics show that the incidence of death from bleeding ulcer is variable, surgical treatment with its high mortality is rarely indicated. It should be considered in cases of a long standing, indurated ulcer which predisposes to erosion of an artery.

Smithies<sup>19</sup> has presented in some detail what he believes to be the necessary treatment for massive gastroduodenal hemorrhage. The immediate therapy is morphine, and no drug is so valuable in physiologic doses. Large injections, i. e., up to from  $\frac{1}{2}$  to 1 grain (0.03 to 0.06 Gm.) every two or three hours for several doses, are often required. A patient in shock should receive intravenously one-third or one-fourth the usual amount of morphine given subcutaneously, in order to avoid a delay in absorption. The foot of the bed should be raised. The blood pressure and blood count should be determined immediately.

If vomiting is copious and if large blood clots are expelled, thorough lavage with physiologic solution of sodium chloride at a temperature of 110 F. is indicated in order to put the stomach at rest. The heat of the lavage solution acts as an admirable hemostatic agent. Local applications of ice to the abdomen are detrimental, but hot moist applications over a bleeding focus are favorable. *Feeding by mouth in all its aspects should be strictly interdicted.* The ingestion of food stimulates peristalsis and tends to interfere with the formation of a permanent clot. "Ulcer diets" can be productive of only harmful effects, and the administration of hemostatic agents by mouth also is contraindicated. Nothing by mouth except sips of hot water for at least two days after all evidence of bleeding has disappeared is the rule. The fluid content of the body can be kept up by the known available routes.

For more than twenty years the author has employed a nutrient enema containing salt solution, dextrose syrup and 50 per cent alcohol. Not until two days after the cessation of hemorrhage is food by mouth

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19 Smithies, F. The Treatment of Massive Gastro-Duodenal Hemorrhage, *Am. J. Digest. Dis. & Nutrition* 1:803, 1935.

permitted and then primarily carbohydrate and no protein. Little milk is administered, and what is given is citiated or parboiled.

If a patient has had one severe hemorrhage he is potentially a subject for surgical treatment. The stoppage of bleeding by drugs has not been successful, and it may lead to a false sense of security. In the author's experience the most potent agent to stop bleeding from a "spurter" is the intravenous administration of 20 cc of a 5 per cent solution of calcium chloride or better still prompt transfusion of a large amount of whole blood. If such measures do not control the bleeding within from thirty-six to forty-eight hours, surgical intervention should be urged without further delay, while the danger involved is still moderate. Roentgen examination should not be attempted for at least four weeks after the cessation of hemorrhage.

In an article entitled "Treatment of Haematemesis and Melaena with Food. The Mortality," Meulengracht,<sup>20</sup> of Copenhagen, Denmark, has presented the results he has obtained in 251 cases of peptic ulcer. His reasons for abandoning treatment by starvation and "very cautious feeding" and adopting the "something to eat" regimen were as follows: (1) an exhausted patient may die after a hemorrhage, (2) protracted hemorrhage sometimes stops when the patient is given food and (3) an ambulant patient often recovers from severe melena without changing his diet. Also it seems of questionable value to starve the patient and allow acid gastric juice to collect in an empty stomach. The diet, which is started on the first day of hospitalization, is described in detail. It consists largely of tea, bread, cereals, cheese, eggs, meats, soft vegetables and fruits and rice and tapioca puddings. The patient is fed five times between 6 a. m. and 6 p. m. and is allowed to eat as much as he wishes. Alkalis with hyoscyamus and iron are given three times a day.

Transfusion was necessary in only 12 cases. There were only 3 deaths in this entire series, and 1 of the patients died before the diet could be started. If this case is not included, the mortality was only about 1 per cent. This rate is far lower than that in any other comparable series of cases in any country, as the mortality usually ranges from about 8 to 20 per cent with the ordinary forms of treatment. Hemorrhage is apparently not aggravated by putting an abundance of food in the stomach, possibly because in most cases the bleeding has already stopped with the giving of this diet. Blood appears less persistently in the stools. The patient is well fortified with nourishment by the eighth day after the onset of bleeding, a time when many die, presumably from exhaustion. Recovery from the state of shock is more rapid, and the regeneration of blood proceeds more quickly. Dyspeptic symptoms clear up early, and the patient's stay in the hospital is materially shortened.

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<sup>20</sup> Meulengracht, E. Treatment of Haematemesis and Melaena with Food. The Mortality, *Lancet* 2: 1220, 1935.

MacGuire<sup>21</sup> has presented a concise review of the present day methods of treating bleeding gastric and duodenal ulcer. Emphasis is laid on the value of massive transfusions of 1,000 cc of whole blood. If this addition to the medical treatment is not successful, operative intervention is indicated. From the standpoint of the surgeon the most important step in dealing with persistent bleeding is to confine his efforts to arrest of the hemorrhage, since a second stage operation eliminates the cause. The possibility of complicating alkalosis with a low chloride and a high urea content of the blood or of vitamin C deficiency with "preclinical scurvy" should not be forgotten.

Hendon<sup>22</sup> advocates the use of continuous venoclysis of dextrose and salt solution for as long as ten days in the treatment of hemorrhage from peptic ulcer. No food is given. He feels that the stomach is put completely at rest by this method of nourishing the patient and that retraction of the clot in the stomach or duodenum is thereby promoted. His results were good in a small series of cases.

Hinton<sup>23</sup> has analyzed 87 cases of massive hemorrhage from peptic ulcer in the hope of giving a more intelligent understanding of the treatment to be employed. It seemed advisable to divide the cases into five groups. In group 1 were 16 patients who bled freely while under competent medical management. Statistics show that with the present trend toward the conservative treatment of peptic ulcer there has been an increase in the incidence of gross hemorrhage. These patients should be operated on when the general condition warrants, as further medical treatment seems futile. In group 2 were 11 patients who first had hemorrhage months or years after a previous operation for acute perforation or chronic ulcer. Under these conditions further treatment should be conservative unless persistent bleeding forces an operation.

Group 3 included the most difficult type of patient to treat, as it consisted of 5 who had been operated on for hemorrhage and who had continued to bleed. One must be guarded in recommending further surgical intervention in such cases. Group 4 included 17 patients in whom severe hemorrhage occurred as the first and presenting symptom. Such an acute hemorrhage is a great menace to life, and over 50 per cent of these patients died despite the usual medical treatment. None of those who recovered had been readmitted to the hospital because of further bleeding. The fifth and largest group consisted of 38 patients

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21 MacGuire, D. P. Bleeding Gastric and Duodenal Ulcers, *Am J Digest Dis & Nutrition* **2** 431, 1935.

22 Hendon, G. A. Treatment of Hemorrhage Caused by Peptic Ulcer, *Am J Digest Dis & Nutrition* **2** 255, 1935.

23 Hinton, J. W. Massive Hemorrhage in Peptic Ulcer, *Ann Surg* **101** 856, 1935.

who were admitted to the hospital with hemorrhage and who had a long history of symptoms of ulcer without regulated treatment. Here conservative management is by far the best method of therapy.

Westermann<sup>24</sup> has discussed the surgical aspects of gastroduodenal ulcer complicated by hemorrhage in 50 patients who had been treated over a recent ten year period. The incidence of heavy bleeding was 12 per cent. Massive and recurrent hemorrhages occurred in three fourths of the patients, and to all of these transfusion was given at least once and usually more often. Transfusion was completely ineffectual as a means of stopping hemorrhage, as 10 patients in this series died while in the hospital under rigid medical treatment, in many cases receiving daily transfusions. This has led to the author's opinion that immediate surgical intervention of the direct type is justifiable in a large percentage of cases and will prove permanently successful, preoperative and postoperative transfusion being an essential requirement.

Twenty-six patients are well, 7 have had one or more recurrences and 8 have died. In 26 cases a total of 42 operations were performed in an attempt to stop the bleeding. Posterior gastro-enterostomy was the operation elected in 17 cases. In several of these cases an ulcer or a scar was identified on the anterior surface of the duodenum at the time of operation, and every one of the patients suffered a recurrence of bleeding. Recurrent hemorrhage developed after twenty-four of the operative procedures employed, and death occurred as a direct result of operation or hemorrhage following surgical treatment in 32.5 per cent of the cases. Resection of the ulcer-bearing area seems to be the operation of choice, but this may be preceded by jejunostomy for arrest of the hemorrhage. There are some interesting discussions of this paper which serve as a nice balance for it and should be read.

In reviewing the cause of death in cases of massive hemorrhage from peptic ulcer, Christiansen<sup>25</sup> has noted that sudden death is rare, and, barring other causes of death such as pneumonia or peritonitis, the patient usually succumbs two weeks after the onset of bleeding. In 12 cases autopsy revealed erosion of a fairly large artery, and the time of death varied between three and thirty days. In the majority of cases there was no evidence of active bleeding. In such cases hemorrhage itself could not have been the cause of death in the more strict sense of the term. The true cause of these "late" deaths is obscure, and in Denmark it has been ascribed to "heart exhaustion." The author suggests that some of these patients die of uremia of extrarenal origin and presents 2 case reports to substantiate this assumption. Both of his

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24 Westermann, J. J. Surgical Aspects of Bleeding Gastric and Duodenal Ulcer, *Ann Surg* **101** 1377, 1935.

25 Christiansen, T. Uremia as Cause of Death in Massive Hemorrhage from Peptic Ulcer, *Acta med Scandinav* **85** 333, 1935.

patients showed marked retention of urea and achloruria following gastric hemorrhage without initial vomiting and without evidence of renal disease. The intake of fluid was adequate. Clinical improvement and a fall in the blood urea content occurred after the administration of a solution of sodium chloride. One patient died on the fifteenth day, but autopsy revealed no evidence of gastro-intestinal bleeding. Death was considered to be due to "gastric uremia." Such a diagnosis is clearly evident in patients with persistent vomiting and loss of chlorides, but these 2 patients did not fall into that category. The exact cause of the achloruria and retention of urea in the blood of the patient who has had copious hemorrhages from a peptic ulcer remains unknown, but evidently uremia occurs and may prove fatal.

Konjetzny<sup>26</sup> has given considerable details in describing his experience not only with the surgical treatment of gastroduodenal ulcer but particularly in treating patients who have been operated on unsuccessfully for this disorder. He has laid special emphasis on the postoperative care of the patient with jejunal ulcer. Primary gastroduodenal resection was performed 106 times and 31 operations were performed in cases in which gastro-enterostomy had previously been carried out.

Two patients were admitted to the Coney Island Hospital, Brooklyn, with the diagnosis of obstructive anuria. Neither complained of any gastro-intestinal symptoms, and both had pain in the lower portion of the abdomen. Both were thought to have retention of urine with rupture of the bladder and were operated on. The first patient proved to have a perforating cancer of the stomach, and the second had a perforating ulcer. Segal and Read<sup>27</sup> in reporting these cases emphasize that complete anuria was the presenting and sole complaint in these cases of perforating gastric lesion, and they suggest that it was due to dehydration secondary to the loss of fluids into the peritoneal cavity by way of the gastric opening.

Another adjuvant to the treatment of a benign peptic lesion has now been added to the lengthy list previously recorded. Rivers<sup>28</sup> has prepared a duodenal extract from the mucosa of the hog and has administered it to 8 patients suffering from gastric or duodenal ulcer. The rationale of this form of therapy is based on three different physiologic principles. First, the duodenal mucous membrane possesses a protecting

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26 Konjetzny, G. E. Erfahrungen bei der chirurgischen Behandlung des Magen-Duodenumgeschwurs und operativer Misserfolge bei diesem, besonders des *Ulcus postoperativum jejunum*, *Arch f klin Chir* **182** 685, 1935.

27 Segal, A. D., and Read, J. S. Complete Anuria in Perforated Gastric Lesions, *Am J Surg* **30** 276, 1935.

28 Rivers, A. B. The Use of Duodenal Extract as an Adjuvant in the Treatment of Benign Peptic Lesions. Report of Eight Cases, *Am J Digest Dis & Nutrition* **2** 189, 1935.

mechanism against acid gastric secretions. Second, it contains a substance which stimulates the flow of alkaline bile, and pancreatic juice, which neutralize acid chyme. Third, the recent work of a number of investigators suggests that intestinal mucosa contains a substance which is absorbed and causes inhibition of gastric secretions. As Rivers used this duodenal extract only as an adjunct to the usual forms of treatment, it is impossible properly to evaluate its efficacy, even though his patients did unusually well. From a physiologic point of view this therapy deserves further trial with a larger group of patients under more carefully controlled conditions.

Sequelae of peptic ulcer following both medical and surgical treatment are all too frequent, and their exact nature all too often goes unrecognized. Hinton<sup>29</sup> has called attention to these facts and has reported on 7 interesting cases illustrating them. Particular attention is paid to the incidence of pancreatitis and the difficulties encountered in making an early diagnosis of such an associated disease. The laboratory lends no aid. In the advanced stages a history of changing symptomatology is most important. Pain is more intense and more constant and radiates through the back to both lumbar regions, where tenderness may be elicited. Cases of chronic gastrojejunal ulceration and gastrojejunal colic fistulas also are illustrated. Such sequelae require prompt surgical attention. The author's conclusions should be memorized by every physician. He states "There is no condition in medicine at present in which clinical judgment plays such an important part in the selection of the method of treatment for the patient as it does in peptic ulcer. Whether the treatment should be medical or surgical is a decision that is based to a great extent on clinical experience."

Pack and McNeer<sup>30</sup> have reviewed the literature on sarcoma of the stomach and add 9 new cases of their own to the 335 recorded up to 1931. Lymphosarcoma is the commonest form and makes up about 40 per cent of the cases. Spindle cell sarcoma and myosarcoma are relatively frequent. The average age of onset is at 46 years, eight years earlier than in carcinoma of the stomach. Also in contradistinction to carcinoma, sarcoma of the stomach is radiosensitive, and roentgen therapy has given some excellent results. Three of the authors' 9 patients are living six, seven and ten years, respectively, after diagnosis of the condition, 2 having had gastric resection and 1 having had roentgen treatment alone.

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29 Hinton, J. W. Sequelae of Peptic Ulcer Following Medical and Surgical Treatment, *Arch Surg* **31** 137 (July) 1935.

30 Pack, G. T., and McNeer, G. Sarcoma of the Stomach. A Report of Nine Cases, *Ann Surg* **101** 1206 1935.

Thompson and Howells<sup>31</sup> report 4 new cases of lymphogranuloma of the stomach and list 11 others from the literature in which treatment by partial gastrectomy was successful. One of the authors' patients was alive and well fourteen years later.

Hodgkin's disease of the stomach is rare. As primary isolated lymphogranulomatosis of this organ it is extraordinarily uncommon, only 7 cases having been recorded in the literature up to 1935. Comando<sup>32</sup> has now recorded in excellent detail an eighth case. His patient was a man 27 years old who had suffered from epigastric pains for three years before he was first seen, on April 26, 1930. The lymph glands and spleen were not palpable. The blood count was normal. Roentgenograms of the stomach showed an infiltrating lesion of the pars media and the pyloric region. Partial gastrectomy was performed. Histologic examination of the tissue removed proved the diagnosis to be Hodgkin's lymphogranuloma. The patient has been perfectly well since then. This report emphasizes that Hodgkin's disease of the stomach may be amenable to operative treatment.

Jones and Carmody<sup>33</sup> have reported a case of lymphosarcoma of the stomach in a child 9 years of age who was operated on and who reported nineteen years later that he was in excellent health. The authors state that survival in this case had been longer than in any case on record and that sarcoma of the stomach has been reported in only 3 other children in this age group. A review of the literature shows that, although lymphosarcoma of the stomach is considered highly malignant, there are a number of cases on record in which the patient lived for more than five years, which is a better outcome than for patients with other forms of sarcoma.

The blood picture characteristic of pernicious anemia has already been recognized as occasionally being noted in association with carcinoma of the stomach. It may be associated with or may be due to benign or malignant polyps arising from the gastric mucosa. Priestley and Heck<sup>34</sup> have reported 3 illustrative cases of bleeding malignant polyps of the cardia which appeared to be instances of pernicious anemia. The tongue was smooth, and the neurologic findings were typical of subacute combined sclerosis of the spinal cord. In the first case there was a single large polyp of the cardia which proved at opera-

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31 Thompson, T, and Howells, L. H. Primary Lymphogranuloma of the Stomach. A Report of Four New Cases, *Quart J Med* **28** 81, 1935.

32 Comando, H. N. Primary Isolated Lymphogranulomatosis of the Stomach. Report of a Case, *Arch Surg* **30** 228 (Feb) 1935.

33 Jones, T. E., and Carmody, M. G. Lymphosarcoma of the Stomach. Report of a Case with a Nineteen-Year Surgical Cure, *Ann Surg* **101** 1136, 1935.

34 Priestley, J. T., and Heck, F. J. Bleeding Malignant Polypoid Lesions in the Cardia of the Stomach, *Ann Surg* **101** 839, 1935.

tion to be carcinomatous. The severe anemia responded well to injections of liver extract, and the patient's condition was much improved. In the second case operation revealed multiple gastric polyps proximal to the incisura. Segmental resection was performed, and the patient's condition was improved. The third patient was at first successfully treated for pernicious anemia. Subsequent gastric analysis revealed a quantity of fresh blood, and further roentgen examination revealed a small polyp. At operation the tumor was removed and found to be a polypoid adenocarcinoma. About fifteen months later the patient was well. It was felt that in these 3 patients pernicious anemia was not due to hemorrhage but was coexistent with the carcinoma.

Results of operation for gastric cancer are always of interest, as medical treatment has little to offer. Consequently a late follow-up of 184 patients with carcinoma of the stomach surgically treated at the Mayo Clinic from 1918 to 1931 gives a good insight into the desirability of abdominal exploration. An unusually extensive resection (subtotal gastrectomy) was performed in each case. In 40 cases in which a preoperative roentgenographic diagnosis of a doubtfully operable lesion was made, the lesion was resectable. Thiessen<sup>35</sup> reports that 33 of these 184 patients, or 18 per cent, were living and well five or more years after the operation. It is of further interest that in half of these patients there was involvement of the lymph nodes at the time of the resection.

#### DUODENUM

Meulengracht has already shown in a series of papers that the anti-anemic factor in pig stomach which is effective in pernicious anemia is presumably confined to the pyloric glands and is not in the peptic glands of the region of the fundus. It is present also, although in smaller quantities, in the cardiac glands. In a fifth communication on preparations from the duodenum this author<sup>36</sup> has demonstrated that the same antianemic substance is present in dried preparations of pig duodenum and that it possesses a powerful antianemic activity. It is evidently associated with the Brunner glands, which are identical with the pyloric glands, and the author suggests that the pyloric-duodenal region which produces this substance should be known as "the pyloric gland organ." Its presence in the duodenum is of great significance as a probable explanation of why pernicious anemia does not develop in all patients with achylia gastrica and in all patients who have been subjected to gastrectomy.

35 Thiessen, N. W. Results of Subtotal Gastrectomy, Proc. Staff Meet., Mayo Clin. **10** 582, 1935.

36 Meulengracht, E. Continued Investigations on the Presence of the Anti-Anaemic Factor in Preparations of Dried Stomach Substance from the Cardia, the Fundus and Pylorus, and the Duodenum, Acta med. Scandinav. **85** 79, 1935.



In a paper entitled "Incidence and Significance of the Roentgenologic Niche in Duodenal Ulcer," Burch,<sup>37</sup> of the Mayo Foundation, has tried to shed further light on a moot question. The incidence of a niche as reported by different observers has varied tremendously, the figures ranging from 13 to 90 per cent. In the previous fifteen months 1,489 cases of roentgenologically diagnosed duodenal ulcer were studied at the clinic, and a definite niche was noted in only 17.7 per cent. Compression roentgenography had not added to the percentage obtained by routine examination in their hands. As Berg's incidence of 50 per cent was based on cases in which operation was performed, the necropsy observations were analyzed for 140 subjects with 176 ulcers. Healed ulcers only were present in 67 cases. Only 40 of the whole series of patients, or 22.7 per cent, had a crater capable of exhibition roentgenologically as a niche. The significance of the niche is threefold. First, it is pathognomonic of ulcer. Second, it is practically an unequivocal sign that the ulcer is active. Third, if it diminishes or vanishes, that is indicative of progress or cure.

The frequency of duodenal diverticulum has been little appreciated. Grant<sup>38</sup> has reported its incidence, location and relation to age from autopsy studies. His routine procedure was to fill the duodenum with wax in order to obtain a cast of its structure. In this way he was able to demonstrate a number of diverticula extending into the head of the pancreas which would have eluded detection without this special technic. One hundred and thirty-three subjects were examined, and 15 had a diverticulum of the duodenum. In 4 there were multiple diverticula. All the sacs were of the hernia type, only the mucous membrane with its tunica muscularis mucosae being involved. In all but 1 case the sac sprang from the concave pancreatic portion of the second and third parts of the duodenum and was buried in the substance of the pancreas.

Of 51 persons aged 52 years and under, only 2 had a diverticulum, while of 82 persons over 52 years of age, 13 had a diverticulum. It is evident that diverticulum is much more common after the fifth decade of life and is present in about 1 in every 5 or 6 persons. These figures reported by Grant give an appreciably higher incidence of duodenal diverticulum than any previously given. Photographs of the duodenums of 7 patients are reproduced in the article, including a photograph of the largest diverticulum on record.

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37 Burch, H. A. Incidence and Significance of the Roentgenologic Niche in Duodenal Ulcer, *Proc. Staff Meet., Mayo Clin.* **10** 471, 1935.

38 Grant, J. C. B. On the Frequency and Age Incidence of Duodenal Diverticula, *Canad. M. A. J.* **33** 258, 1935.

In a clinical treatise on this same subject Celice and Parrot-Manson<sup>39</sup> also have noted that diverticulum of the duodenum is frequent late in adult life and that it usually arises from that part of the duodenum adjacent to the head of the pancreas. Symptoms when present are usually associated with peptic ulcer, cholecystitis or pancreatitis.

The cause of obstructive jaundice is often a difficult diagnostic problem, particularly in an older person. In a patient without colic the possibility of a benign lesion is often forgotten, and cancer is considered the responsible agent. Nicholson<sup>40</sup> has called attention to a cause that is often overlooked—that of a diverticulum of the duodenum. His 66 year old patient had suffered from intermittent jaundice for four and one-half months and came to autopsy without operation. Roentgen examination had revealed the diverticulum. Anatomically it arose from the region of the ampulla of Vater and occluded the common bile duct by pressure on it. Similar cases are cited from the literature.

A patient who was apparently suffering from benign tumor of the duodenum is reported on by Roelsen,<sup>41</sup> but the diagnosis is based on repeated roentgen findings alone and not on an anatomic examination. However, the report is of particular value as it contains an outlined summary of 27 cases of benign duodenal tumor, in most cases a polyp, which have been reported in the literature since 1921. The apparent rarity of the lesion and the importance of roentgenograms in the diagnosis are stressed.

#### SMALL INTESTINE

The management of jejunal ulcer and the conditions leading to its production have been the subject of a paper by Donald C. Balfour,<sup>42</sup> of Rochester, Minn. A striking feature of jejunal ulcer is its remarkable similarity to duodenal ulcer both as to symptomatology and pathologic process and as to the complications of hemorrhage, perforation and obstruction. Intensive medical treatment should always be tried in the early stage of the ulcer before operation is considered. The surgical management of jejunal ulcer differs from that of duodenal ulcer in that operative treatment of jejunal ulcer, disconnection of the anastomosis, will bring about a cure in all cases. The important decision at the time of operation is to make sure a jejunal ulcer is present, and while this is usually easy the ulcer may be located on the posterior wall

39 Celice, J, and Parrot-Manson. Les diverticules duodenaux, *Presse med* **43** 1313, 1935

40 Nicholson, W. M. Jaundice Produced by a Diverticulum of the Duodenum, *Bull. Johns Hopkins Hosp* **56** 305, 1935

41 Roelsen, E. Benign Tumors of the Duodenum, *Acta med Scandinav* **84**: 439, 1935

42 Balfour, D. C. Jejunal Ulcer, *Am J Surg* **28** 439, 1935

and may be without indication or evidence of perforation, hence it may be overlooked. In cases of hemorrhage, even if a lesion cannot be palpated, it is good practice to eliminate the anastomosis. Plastic procedures on the anastomosis invite recurrence.

However, in practice the problem of the cure of a jejunal ulcer is of minor importance compared with the control of the disease for which the patient was originally operated on. From this standpoint three types of patients should be considered: (1) those with no primary lesion or with a completely healed ulcer, (2) those obviously requiring surgical management of the primary lesion and (3) those who have already undergone gastric resection. In the first group there is obviously no further need for the gastro-enterostomy, and elimination of the anastomosis is all that is indicated. In the second group the most effective method of controlling the disease is by extensive gastric resection, and this is the operation of choice in treating patients with jejunal or duodenal ulcer. A more conservative operation may at times meet the situation satisfactorily. In the third group, in which gastrectomy has already been performed, the jejunal ulcer should be excised, and the jejunum should be disconnected from the stomach. The stomach may then be reanastomosed to the upper portion of the duodenum. Finally, jejunal ulceration depends largely on the circumstances for which an operation on the primary lesion was performed. Gastro-enterostomy for duodenal ulcer in the case of a young patient with high acidity will be followed by a high incidence of jejunal ulcer.

The remarks on treating duodenal ulcer by gastro-enterostomy which accompany this paper by Balfour are well worth quoting. Frank H. Lahey, of Boston, stated "I would not wish to have a gastro-enterostomy if I could avoid it." J. S. Horsley, of Richmond, Va., said "A young man with high gastric acidity and a duodenal ulcer who has an enterostomy in addition to his other troubles is in a very unenviable condition." J. M. T. Finney, of Baltimore, stated "I have felt that it [gastro-enterostomy] was an essentially unsurgical and unscientific operation."

Under the term primary jejunal ulcer Smith<sup>43</sup> records only those cases in which the lesion was primary in the jejunum and did not follow an operative procedure such as a gastro-enterostomy. Only 25 such cases have previously been described, the author presents each in abstract and adds a report of a case of his own in which the ulcer had perforated. Obstruction alone or in addition to perforation was present in several instances. In all but 3 cases the condition was diagnosed either at operation or at autopsy. In these 3 cases the lesion produced constriction as noted by roentgen examination. Certain symptoms differ

<sup>43</sup> Smith B. C. Primary Perforated Jejunal Ulcer, *Ann Surg* **101** 1225 1935

from those of gastric and of duodenal ulcer. In cases of primary jejunal ulcer the pain is most often in the left upper portion of the abdomen, is nonradiating and appears at no appointed time as regards meals. It is usually made worse by eating, and at no time is it relieved by taking food or soda.

Sjoberg,<sup>44</sup> of Stockholm, reports an unusual case in which there were symptoms of ileus from retention of iron in the cecum. The patient was anemic and had received about 4 Gm. of reduced iron daily for more than two months. Gastro-intestinal symptoms developed, and repeated roentgenograms of the abdomen showed in the cecum a large contrast shadow which was twice the size of a plum. Intestinal evacuations showed iron, and a few stonelike, rather firm lumps also escaped. Subsequent examination showed that only a part of the iron mass had left the cecum, and parts of it could be identified in the colon.

The author was able to produce a contrast shadow in the intestine in another patient by giving large doses of iron, but no symptoms of ileus occurred.

Intussusception of the small intestine in the adult is a relatively uncommon cause of intestinal obstruction and is usually caused by a neoplasm, which is often benign. The literature on this subject is reviewed by Haggard and Floyd.<sup>45</sup> They present an interesting case report of a boy aged 14 years who had three small intestinal resections for intussusception due to adenoma. There was a remarkable family incidence of intestinal obstruction due to a tumor in this case. The boy's father had four operations for obstruction, in three instances the obstruction was due to neoplasm and in the fourth to a malignant polyp of the colon. The boy's only sister had two operations for obstruction due to a benign growth. The familial phenomenon was strikingly illustrated by this family.

Linitis plastica is a rare but long-recognized lesion of the stomach. That it may also involve the intestinal tract is little known. Stevens,<sup>46</sup> of the Mayo foundation, found reports of only 37 such cases in the literature. He found reports of 6 similar cases in the files of the clinic, and he cites 1 in detail in which obstruction of the large bowel led to a fatal termination. One of his patients was alive eleven years after abdominal exploration, but the other 5 all showed microscopic evidence of a malignant growth.

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44 Sjoberg, H. Symptoms of Ileus from Retention of Iron in Cecum Following the Administration of Large Doses of Iron, *Acta med Scandinav* **85** 128, 1935.

45 Haggard, W. D., and Floyd, W. O. Repeated Resections for Intussusception Due to Familial Tumors of the Small Intestine, *Am J Surg* **28** 428, 1935.

46 Stevens, G. A. Carcinoma of the Linitis Plastica Type Involving the Intestine, *Proc Staff Meet, Mayo Clin* **10** 349, 1935.

Haggard<sup>47</sup> in his study on appendicitis has remarked particularly on the delayed operation in delayed appendicitis. He has reviewed the results of 3,344 operations for this disease in his own clinic at the Vanderbilt University School of Medicine and analyzed the literature with particular reference to the lack of improvement in the mortality since the time of Reginald Fitz, fifty years ago. The persistent high incidence of postoperative deaths falls largely in the cases of spreading peritonitis which often follows gangrenous perforation of the appendix. Such a sequela is usual in a case of obstruction of the appendix and may well be compared with that of obstruction of the intestine with its like results. Operation in this stage results in about a 25 per cent mortality.

Theoretically, if every patient with appendicitis could be operated on in the first twenty-four hours the terrible death rate would be a thing of the past. A good surgeon may wisely postpone operation during the "fatal third or fourth day" and may wait until the inflammation has localized or a palpable abscess mass is detectable. There is no conservative treatment in the majority of cases, however, once a purgative has been given. When the patient enters the hospital with a palpable mass, appendectomy and drainage give a mortality of 15 per cent, while drainage alone gives only a 4 per cent mortality. Subsequent appendectomy will be required in about half the latter cases and the death rate is then only a little over 1 per cent. The author emphasizes that appendicitis is an emergency during the first few hours and that operation is indicated at once. Much surgical wisdom must be exercised in deciding for or against opening the abdomen in the cases of delayed development of symptoms, because it is at this time that the great number of fatalities occur following operation.

Schmidt and Taylor<sup>48</sup> wished to compare the conservative and operative methods of treating acute appendicitis. Experimentally they produced acute appendicitis (actually typhlitis) in 48 dogs by ligating arteries or crushing or ligating the base of the organ. Twenty-eight animals survived, 13 of these were operated on, while the rest were given conservative treatment. There was a mortality of only 29 per cent in this second group, while the mortality in the group operated on for acute appendicitis was 52 per cent, the cause of death being peritonitis in the majority of cases. The authors conclude that in dogs the conservative treatment of acute appendicitis shows a lower mortality than operative treatment.

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47 Haggard, W. D. Appendicitis. An Analysis of 3,344 Cases with Remarks on the Delayed Operation in Delayed Appendicitis, *Am J Surg* 28:71, 1935.

48 Schmidt, E. R., and Taylor, A. C. Acute Appendicitis in Dogs, *Arch Surg* 31:65 (July) 1935.

A case of a rare condition recognized in German literature under the name pneumatosis cystoides intestinalis has been described by Graberger<sup>49</sup> because he felt that the correct diagnosis could have been made by roentgen examination if that condition had been kept in mind. In cases previously reported on the condition was recognized only at operation or at autopsy. The author's case is the first one in which roentgen studies were made which could be called diagnostic. The cause of these air-containing cysts, which also occur in swine, sheep and chickens, is thought to be bacterial, or, what is more likely, to be due to entrapped air which has entered the loose areolar tissue of the abdomen. The cysts are located in the mesentery, in the omentum under the diaphragm and on the peritoneum and are usually multiple and grapelike. Most of the patients have symptoms of ulcer and often of pyloric stenosis as well.

The author's patient was a woman 39 years old with symptoms suggesting peptic ulcer complicated by pyloric obstruction. Roentgenograms confirmed the clinical impression, and operation proved the diagnosis to be correct. The surgeon found also a 50 cm portion of the lower end of the ileum which showed typical pneumatosis. A review of the roentgenograms revealed an area the size of the hand in the left flank with an unusual alveolar structure, the preoperative significance of which was unknown. The film of this area is compared in the article with a film of the specimen removed, and this comparison seems to justify the author's conclusion that a preoperative diagnosis of pneumatosis cystoides intestinalis could have been made by roentgenologic examination.

#### LARGE INTESTINE

A J Baker has translated into English the thesis entitled "Vaccine Therapy in Ulcerative Colitis" by Sibrand Lups,<sup>50</sup> of Groningen, Holland. Actually the title is too limited in its scope, as the first part of this thesis deals entirely with the clinical and roentgenologic aspects of the disease and will serve for a long time to come as one of the best monographs on this subject which has yet been written. There is a brief historical review, as well as excellent descriptions of the symptoms and signs, the disturbances in the defecation, the findings in the stools, the examination of the rectum and the sigmoid flexure, the blood picture and the medical and surgical treatment. The outstanding feature of this clinical description is the section on roentgenography. Findings in the catarrhal, ulcerative, nodular hyperplastic and healing stages are discussed and illustrated by pictures which must be seen to be appreciated.

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49 Graberger, G. Beitrag zur Kenntnis des Roentgenbildes bei Pneumatosis cystoides intestinorum, *Acta radiol* 16 439, 1935.

50 Lups, S. Vaccine Therapy in Ulcerative Colitis, *Am J Digest Dis & Nutrition* 2 65 and 139, 1935.

In the second part of this thesis the author has reviewed the bacteriology of idiopathic ulcerative colitis, with particular emphasis on the work of Baigen with his vaccine therapy. Baigen's diplococcus was injected into 15 rabbits. Most of the animals showed a loss of weight and diarrhea, and at autopsy the lumen of the bowel contained bloody mucus. In nearly all the rabbits the diplococcus was present in the blood stream from forty-eight to seventy-two hours after the injection and was present also in the intestinal mucus. Control animals remained normal. The conclusion is that the diplococcus is able to cause inflammation of the cecum and colon. The strain of organism used was apparently a virulent one.

Case histories are presented of 16 patients who were treated with diplococcus vaccine. Eight recovered completely, and 6 others were improved. These results of autovaccination are concisely outlined in tabular form. Special cultural methods were used for growing the diplococci, greatly facilitating their recovery from the infected colon.

There is little information available as to the exact prognosis of non-specific ulcerative colitis. The fact that the earlier clinicians called it colitis gravis gives a good insight into what the ultimate course may be. Consequently the follow-up studies of 90 cases of this disease by Crohn and Rosenak<sup>51</sup> are particularly timely. The cases were followed for from two to fourteen years, and the records are up to date in 75 cases. Approximately half the patients had been ill for less than a year and the other half for from two to fourteen years. Of the 90 patients, 44.5 per cent are listed as cured, 29.9 per cent as improved, 10.9 per cent as unimproved and 14.8 per cent as dead. Seventy-five per cent of the entire group were cured or improved. The longer the cases were followed the lower the percentage of favorable results. However, the rate fell only to 62 per cent in the group followed for from six to ten years.

Certain general rules of treatment were followed in all cases. A retention enema of a 1:4,000 solution of acriflavine base in physiologic solution of sodium chloride was usually given nightly. Colonic irrigations were avoided. The diet was liberal and included in all classes of vitamins. Deodorized tincture of opium was employed for excessive diarrhea but in minimal amounts. Since 1921 the intravenous injection of polyvalent antidysentery serum has been employed, but it is recognized that any protein shock and febrile reaction could bring about a beneficial change in the chronic course of the disease. Splendid results followed the authors' method of treatment with a specific serum. It is comparable to Baigen's results with a streptococcus vaccine and serum.

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<sup>51</sup> Crohn, B. B., and Rosenak, B. D. A Follow-Up of Ulcerative Colitis (Non-Specific), *Am J Digest Dis & Nutrition* 2:343, 1935.

For surgical treatment ileostomy is the operation of choice, but it should be restricted to cases in which the condition is regarded as incurable under any form of medical therapy. The mortality was 33.5 per cent. The conclusion is that *skilful neglect does not succeed in cases of ulcerative colitis*. A strict and aggressive therapeutic program will bring favorable results in a large percentage of cases in which the condition is supposedly incurable.

As the name of the disease implies, the cause of idiopathic ulcerative colitis remains obscure. It has been stated repeatedly that this condition may be related to bacillary dysentery. Winkelstein and Herschberger<sup>52</sup> have explored the possibilities of this relationship from three points of view. One hundred and twenty patients with nonspecific ulcerative colitis were tested for the presence of the dysentery bacillus, for positive agglutinations with this organism and for a bacteriophage active for one or more strains of the dysentery bacillus group. *Bacillus dysenteriae* was present in 7 of 60 cases. Positive agglutinations were present in high titer in 27 cases (22 per cent of the whole series). Even further suggestive, if indirect, evidence that these patients have or have had bacillary dysentery is to be found in the identification of a bacteriophage active for dysentery organisms in 36 per cent of 41 cases. The therapeutic implications of these findings are clear, but the treatment of ulcerative colitis with polyvalent antidysentery horse serums has not yet been established as superior to other forms of treatment with foreign protein shock. Bacteriophage therapy is now on trial. These studies suggest that bacillary dysentery may play an etiologic rôle in some cases of nonspecific ulcerative colitis.

After surgical treatment of the colon fatal peritonitis is probably more common than after any other type of abdominal operation. Intraperitoneal vaccination has been introduced in an endeavor to lower the mortality. In the earlier methods it was the aim to produce leukocytosis, but no striking protection of the peritoneum was obtained. At present living bacteria or a vaccine of heat-killed colon bacilli and streptococci is injected intraperitoneally. In this type of vaccination a true immune process occurs in which the peritoneum shares locally, and its protection is thought to be due to local hyperleukocytosis. A number of days pass before this takes place. It is to be borne in mind that the use of a vaccine is only prophylactic and not curative and that it is contraindicated in the presence of peritonitis.

Potter and Coller<sup>53</sup> used a heat-killed *Bacillus coli* vaccine approximately forty-eight hours before operation on the colon in 79 cases.

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<sup>52</sup> Winkelstein, A., and Herschberger, C. Studies on the Relation of Non-Specific Ulcerative Colitis to Bacillary Dysentery, *Am J Digest Dis & Nutrition* **2** 408, 1935.

<sup>53</sup> Potter, E. B., and Coller, F. A. Intraperitoneal Vaccination in Surgery of the Colon, *Ann Surg* **101** 886, 1935.



Two hundred million bacilli were suspended in 1 per cent tragacanth in physiologic solution of sodium chloride prepared in ampules of 30 cc each. This preparation diffuses extensively through the peritoneal cavity and is not absorbed too rapidly. In most cases fever and pronounced leukocytosis developed. At operation 73 per cent of the patients showed definite hyperemia of the bowel, omentum and mesentery, an increased amount of peritoneal fluid was present in 31 per cent, and in 24 per cent a true exudate occurred with the appearance of generalized peritonitis. Although 11 patients died, in only 1 instance was death due to peritonitis. Such a low incidence of peritonitis seems to justify the use of the vaccine as a valuable adjunct in the preparation of a patient for an operation on the colon. Its usefulness is in protecting the peritoneum against minor degrees of soiling and infection, but not against gross fecal contamination.

Spontaneous perforation of a diseased ulcerated cecum is well recognized, but it is not generally realized that a diastasic perforation, or "blow out," of an overdistended but otherwise normal cecum may occur as a result of distal obstruction. Few such cases have been described, but Saeltzer and Rhodes<sup>54</sup> have reported 5 instances of this unusual and dramatic accident. Four of these were due to cancer involving the sigmoid flexure, one of which was extrinsic from the ovary and another to cancer of the splenic flexure. They conclude that necrosis and perforation are most often due to some vascular impairment dependent on a preceding infectious process, and the medial wall is the usual site of the break because it is mechanically weaker. In 1 of their cases the obvious tear was apparently due to mechanical violence alone.

In 2 reports, 1 on the colon and 1 on the rectum, Raiford<sup>55</sup> has presented a complete analysis of carcinoma of the large bowel. Five hundred and eleven patients admitted to the Johns Hopkins Hospital in the forty-two year period since 1889 were observed. In 192 cases the lesion was in the colon and in 319 in the rectum. In 72 cases it was located in the descending colon and sigmoid flexure and in almost as many, 67, in the cecum and ascending colon. Five year postoperative "cures" were obtained in 32.2 per cent of the cases of operable carcinoma of the colon and in 23.2 per cent of the cases of rectal carcinoma. As the analysis is presented in detail and reveals a number of important facts, the original papers should be used as an up-to-date reference on this subject.

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54 Saeltzer, D. V., and Rhodes, G. K. Diastasic Perforation of the Normal Cecum Resulting from Obstruction of the Normal Colon, *Ann Surg* **101** 1257, 1935.

55 Raiford, T. S. Carcinomas of the Large Bowel, *Ann Surg* **101** 863, 1935.

Under the title "Simple Hemorrhagic Proctitis and Proctosigmoiditis" Thaysen <sup>56</sup> has described a condition of the lower bowel which occurs relatively frequently but which has received no recognition until recently. It is not to be confused with an ulcerative condition and is limited to the sigmoid flexure and rectum. The bleeding is usually thought to be due to hemorrhoids, and rectoscopy is imperative for an accurate diagnosis. Direct inspection of the rectal mucous membrane when the inflammatory condition is fully developed shows it to be swollen, deep red and finely granular. It bleeds easily. No ulceration or distinct erosions were noted in the 20 patients examined by the author. Microscopically the mucous membrane is the site of marked cellular infiltration and greatly engorged vessels, but abscess formation and necrosis are absent. The accompanying figures illustrate the lesion nicely. Stenosis and thickening of the rectal wall do not occur even in cases of involvement of long standing.

This form of proctitis is most common in young adults. The one common symptom is free bleeding in small amounts, ordinarily accompanying the stool. As the disease is chronic and recurrent some purulent mucus may appear. Slight constipation is the rule. In cases in which the condition is uncomplicated there are no other symptoms, and fever rarely occurs. Rectal examination reveals only blood and mucus on the examining finger and the absence of hemorrhoids which might be held responsible for the symptoms. Blood may be on the outside of a lumpy stool, or it may follow its passage and be entirely separated from it. Anemia is only moderate, if present, despite the long duration of the disease and the repeated hemorrhages. Gastric analysis and roentgen examination are of no aid in the diagnosis, which must be based on rectoscopy. Confusion with hemorrhoids, polyposis or ulcerative colitis can be cleared up only by direct inspection of the wall of the lower portion of the large bowel. The etiology of simple hemorrhagic proctosigmoiditis is unknown. In Denmark this condition occurs more frequently than ulcerative colitis.

The treatment is partly local and partly general. Local instillations of a 1 per cent solution of chiniofon produces good immediate results which may be striking. Such treatments must be given daily for an average of two months. In some cases this form of therapy may fail, and relapse often occurs later. General treatment consists of rest in bed, sedatives and the combating of constipation. As regards the prognosis, no patient has died, serious relapses are rare in the cases in which treatment is instituted, and the patient who has had a mild relapse responds well to therapy. However, a relapse may occur even after the patient has been free from bleeding for four years.

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<sup>56</sup> Thaysen, E. H. Simple Hemorrhagic Proctitis and Proctosigmoiditis. *Acta med Scandinav* 84 1, 1935.

## INTESTINAL PARASITES

Intestinal infestation with *Giardia intestinalis* is not rare among the inhabitants of the temperate zones MacPhee and Walker<sup>57</sup> have studied the pathogenicity and symptomatology of the infection caused by this parasite in a series of 732 patients observed in New England This miscellaneous group of patients presented a variety of gastro-intestinal complaints, and routine examination of the biliary drainage was made in each case *Giardia* were present in only 6 cases, an incidence of slightly less than 1 per cent Perhaps in the majority of cases the infection may occur without causing complaints which might lead to their detection Five of the authors' cases are presented, but therapy was carried out to eradicate the parasites in only 1 instance This patient's condition was improved The authors present some important conclusions based on their own studies and on a review of the literature

A variety of symptom complexes occur, but in the cases of more severe involvement they are more biliary than intestinal In almost all instances there are nausea and pain of varying severity in the upper portion of the abdomen, less frequently there are jaundice, enlargement of the liver and tenderness of the gallbladder There is no accompanying eosinophilia The gallbladder has been removed in many cases without affording relief from the symptoms Microscopic examination of fresh duodenal contents readily reveals the parasites Stool examinations are less successful Giardiasis should be considered in all cases in which cholecystectomy for chronic cholecystitis or cholesterosis seems indicated but in which there is no definite evidence of gallstones

Although there are many statements to the contrary, *Giardia* is clinically pathogenic Usually the habitat of the organisms is limited to the duodenum and jejunum, but they have been demonstrated in the bile ducts and in the gallbladder Various forms of antiprotozoa therapy have been successful The authors used thymol A reduction in the number of organisms will alleviate the symptoms, but cure by means of their complete eradication is rare

G S de Paula e Silva,<sup>58</sup> of Bello-Horizonte, Brazil, has presented a clinical study of 22 patients with giardiasis seen in private practice These represent 3.8 per cent of 572 patients seen over a two year period The incidence of this parasitic infestation is thought to be much higher in clinic patients (i e., the poor) The diagnosis was based on the presence of *Giardia* (*lamblia*) in the bile obtained by duodenal drainage

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<sup>57</sup> MacPhee, L., and Walker, B. S. Intestinal Giardiasis in New England, with Notes on Its Pathogenicity and Symptomatology, *Am J Digest Dis & Nutrition* 1 768, 1935

<sup>58</sup> de Paula e Silva, G. S. A Clinical Review of Giardiasis Twenty-Two Cases Observed During Study of Five Hundred and Seventy-Two Private Patients, *Am J Digest Dis & Nutrition* 2 350, 1935

Cysts of *Giardia* were present in the stools in only 54 per cent of the cases, when only one specimen was examined. In 1 instance fifteen repeated stool examinations gave negative results.

Certain symptoms were so frequent in these patients and so constantly disappeared after eradication of the parasites that, contrary to the common belief, the author feels that intestinal infestation with *Giardia* causes definite symptoms. These have been divided into three groups: those attributable to involvement of the biliary tract, with dyspepsia and severe pains like gallstone colic, those suggesting extensive infestation of the intestine, with diarrhea often a feature, and those which are polymorphous and systemic. Two patients had high fever. One presented jaundice, but it was not attributable to giardiasis. The author insists that giardiasis should be treated and outlines his technique in detail. After good drainage of the biliary tract, neoarsphenamine is given intravenously at five day intervals for from twenty to twenty-five days. During this time acetarsone and chiniofon are given by mouth. The results of this therapy are good. The condition appears to be clinically cured. Fourteen of 16 patients were free from parasites seven months after treatment. Failure was apparently due to inadequate treatment. The author recognized the possibility that relapses may still occur.

Although infestation with *Ascaris* is usually considered benign, Genkin<sup>59</sup> has described the case of a 12 year old girl with volvulus caused by an enormous mass of the worms which blocked the bowel. Operation was successfully performed, and 800 ascarides were removed. The author states that this is larger than any number of these parasites that has been reported in the literature.

Adams,<sup>60</sup> in Mauritius, has reported an unusual case of ascariasis of the liver in which the patient came to autopsy after exploratory laparotomy for an acute abdominal condition. The hepatic duct was observed to be torn open by the passage through it of an ascaris worm. Seven adult worms were found in the gallbladder and four more in the liver, and numerous eggs were present in the parasitized bile passages.

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59 Genkin, I. I. Ein Fall von Ascariden volvulus, hervorgerufen durch eine enorme Menge von Ascariden, *Arch f klin Chir* **182** 642, 1935.

60 Adams, A. R. D. Ascariasis of the Liver, *Tr Roy Soc Trop Med & Hyg* **28** 419, 1935.

# News and Comment

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## THE AMERICAN BOARD OF INTERNAL MEDICINE, INC

The American Board of Internal Medicine, which was incorporated on Feb 28, 1936, completed its organization on June 15. The officers chosen were Dr Walter L. Bierring, Des Moines, Iowa, chairman, Dr Jonathan C. Meakins, Montreal, Canada, vice chairman, and Dr O. H. Perry Pepper, Philadelphia, secretary-treasurer. These officers and the following six members constitute the present membership of the board: Dr David P. Barr, St. Louis, Dr Reginald Fitz, Boston, Dr Ernest E. Irons, Chicago, Dr William S. Middleton, Madison, Wis., Dr John H. Musser, New Orleans, and Dr G. Gill Richards, Salt Lake City.

The term of office of each member will be three years, and no member may serve more than two consecutive three year terms.

The organization of the board is the result of effective effort on the part of the American College of Physicians in conjunction with the Section on Practice of Medicine of the American Medical Association, and these two organizations are represented in the membership of the board in a five to four ratio.

The American Board of Internal Medicine had previously received the official approval of the two bodies fostering its organization, as well as that of the Advisory Board for Medical Specialties and of the Council on Medical Education and Hospitals of the American Medical Association.

The purpose of the board will be the certification of specialists in the field of internal medicine and the establishment of qualifications with the required examination procedure for such certification.

While the board is at present chiefly concerned with the qualification and procedure for certification in the general field of internal medicine, it is intended to inaugurate immediately after July 1, 1937, similar qualification and procedure for additional certification in certain of the more restricted and specialized branches of internal medicine, such as gastro-enterology, cardiology, metabolic diseases, tuberculosis and allergic diseases. Such special certification will be considered only for candidates who have passed at least the written examination required for certification in general internal medicine. The operation of such a plan will require the active participation and cooperation of recognized representatives from each of such special fields of medicine.

Each applicant for admission to the examination in internal medicine will be required to meet the following standards:

### General Qualifications

1. Satisfactory moral and ethical standing in the profession.
2. Membership in the American Medical Association or, by courtesy, membership in such Canadian or other medical societies as are recognized for this purpose by the Council on Medical Education and Hospitals of the American Medical Association. Except as here provided, membership in other societies will not be required.

### Professional Standing

1. Graduation from a medical school of the United States or Canada recognized by the Council on Medical Education and Hospitals of the American Medical Association.
2. Completion of an internship of not less than one year in a hospital approved by the same council.
3. In the case of an applicant whose training has been received outside the United States and Canada, presentation of credentials satisfactory to the Advisory Board for Medical Specialties and the Council on Medical Education and Hospitals of the American Medical Association.

## Special Training

- 1 Five years must elapse after the completion of a year's internship in a hospital approved for the training of interns before the candidate is eligible for examination
- 2 Three years of this period must be devoted to special training in internal medicine. This requirement should include a period of at least several months of graduate work under proper supervision in anatomy, physiology, biochemistry, pathology, bacteriology or pharmacology, particularly as related to the practice of internal medicine.

This work may be carried on in any domestic or foreign medical school or laboratory recognized by the Council on Medical Education and Hospitals of the American Medical Association as offering appropriate facilities for this type of postgraduate experience, or it may include a period of at least several months of graduate work under proper supervision in internal medicine or in its restricted and specialized branches in any domestic or foreign hospital, clinic or dispensary recognized by the council as offering appropriate facilities for this type of postgraduate experience.

- 3 A period of not less than two years of special practice must be spent in the field of internal medicine or in its more restricted and specialized branches. The American Board of Internal Medicine does not propose to establish fixed rules for the preliminary training of candidates for certification in this field. Broad, general principles for training, however, may be outlined, although such suggestions as are made must, of necessity, be subject to constant changes reflecting the dynamic nature of the specialty.

A sound knowledge of physiology, biochemistry, pharmacology, anatomy, bacteriology and pathology, so far as they apply to disease, is regarded as essential for continued progress of the physician who practices internal medicine. The mere factual knowledge of medicine and its basic sciences is not sufficient. The candidate must have had training in their use in furthering his understanding of clinical medicine. This implies practical experience under the guidance of older men who bring to their clinical problems ripe knowledge and critical judgment. Preparation to meet this requirement adequately may be even more difficult to obtain than the so-called scientific training. It may, however, be acquired in the following ways:

- a By work in a well organized outpatient clinic of a hospital, conducted by competent physicians
  - b By a prolonged period of hospital residency, likewise under the direction of skilled physicians
  - c By a period of training in intimate association with a well trained and critical physician who has taken the trouble to teach and guide his assistant rather than to require him to carry out the minor drudgery of busy practice
- 4 The board does not consider it to the best interests of internal medicine in this country that rigid rules be made as to where or how the training as outlined is to be obtained. Medical teaching and knowledge are international. The opportunities of all prospective candidates are not the same. Some may have the opportunity of widening their knowledge by a period of study abroad, others, at the other extreme, may be restricted to a comparatively narrow geographic area, and their detailed training must be obtained in short periods scattered over a long time. Although it is required that at least five years must elapse between the termination of the first year of internship and the time when the candidate is eligible to take the examination, a longer period is advisable. The board wishes to emphasize that the time and training are but means to the end of acquiring broadness and depth of knowledge of internal medicine which the candidate must demonstrate to the board in order to justify it in certifying that he is competent to practice internal medicine.

as a specialty The responsibility of acquiring the knowledge as best he may rests with the candidate, while the responsibility of maintaining the standard of knowledge required for certification devolves on the board

#### Method of Examination

The examination required of candidates for certification as specialists in internal medicine will comprise part 1 (written) and part 2 (practical or clinical)

Part 1 The written examination is to be held simultaneously in different sections of the United States and Canada and will include

*a* Questions on applied physiology, physiologic chemistry, pathology, pharmacology and the cultural aspects of medicine, and

*b* Questions on general internal medicine

The first written examination will be held in December 1936, and candidates successful in this written test will be eligible for the first practical or clinical examination, which will be conducted by members of the board near the time for the annual session of the American College of Physicians at St Louis in April 1937 The second practical examination will be held at Philadelphia near the time of the annual session of the American Medical Association in Atlantic City, N J, in June 1937

The fee for examination is \$40, which must accompany the application, and an additional fee of \$10 is required when the certificate is issued

Application blanks and further information can be obtained by addressing the office of the chairman, Dr Walter L Bierring, 406 Sixth Avenue, Des Moines, Iowa

## Book Reviews

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**El problema de la infección focal de las amígdalas y su importancia en medicina** Prueba personal para el diagnóstico y técnica más conveniente para la amigdalectomía By Dr Rafael Romero Rodríguez Paper Price, 7 pesetas Pp 165 Seville Imp de la "Divina Pastora," 1935

A page from Dr Romero Rodríguez' clear, though brief, treatise on the tonsils and tonsillectomy when they are the site of focal infection, in which he notes the "100 per cent tonsillectomized portions of the United States" as "an exaggeration appropriate only to that country," might well be translated for the benefit of American tonsil specialists. His careful and time-consuming tests for the proof of tonsillar infection, local or focal, may seem unusual to the average American physician. In order to make a diagnosis of focal infection of the tonsils he depends on (1) the bacterial examination of the caseous material expressed from the crypts, and (2) the test of Viggo Schmidt, a leukocyte count, and the temperature before and after a two minute massage of the tonsils with the finger. If the tonsil is healthy, massage produces leukopenia in about twenty minutes, when infection is present, leukocytosis and a rise in temperature are noted. The Romero tonsil cleansing test is less likely than the Viggo Schmidt test to cause trouble, it is reliable as an aid in making a diagnosis of focal infection in the tonsil. The tonsil is emptied (the open crypts) by massage with a fenestrated depressor and syringed with saline solution. Symptoms that are due to tonsillar infection—low fever, cardiac irritability, myalgia and headaches—disappear and then return after a week or more. If another cleansing is followed by the subsidence and recurrence of the symptoms, one is able to guarantee that benefit will be derived from tonsillectomy. Of course no such test is made during the height of the activity of an infection.

The author's technic of tonsillectomy is one of dissection, as the tonsils he advises to be removed are those characterized by fibrosis, with a prolonged upper pole. Burial of the tonsils under the pillars makes the Sluder method useless. One wonders, however, while reading the excellent description of a disturbing hemorrhage, why it would not be best to finish with one of the crushing technics.

Chapters on disorders due to focal infection in the tonsil (arthritic, renal and allergic) give brief reviews of American and other work. It is clearly stated that the tonsil is the best ally of the streptococcus. The tonsil when acutely inflamed hinders bacterial invasion. This usefulness is lost when it becomes a septic focus. Endocarditic, renal and arthritic conditions subside after tonsillectomy, and cure may be effected. However, these metastases may have sufficient vitality to sustain the infection, especially when their treatment is neglected after tonsillectomy. A list of selected case histories is given.

This is a book that internists and specialists will find worth reading.

**Medical Treatment of Gallbladder Disease** By Martin E. Rehfuss, M.D., Clinical Professor of Medicine at Jefferson Medical College, and Guy M. Nelson, M.D., Instructor of Medicine at Jefferson Medical College. Pp 465, with 113 illustrations. Cloth, \$5.50 net. Philadelphia: W. B. Saunders Company, 1935.

This work is based on experience with 908 patients with disease of the gallbladder who were treated medically during the past ten years. Rehfuss and Nelson, however, give no analysis of data as to the results of such treatment or as to its individual elements. One hundred and twenty pages are devoted to the diagnosis of cholecystitis, much emphasis being placed on the results of duodenal intubation and cholecystography in diagnosis and in observation of the



course in the patient under treatment. The catalog of symptoms described as suggesting cholecystitis leaves one with the impression that various other conditions, mostly functional, may have been included by the authors under the class of mild cholecystitis, and this perhaps helps explain their enthusiasm for medical treatment.

The authors feel that the present knowledge of the physiology and pathology of the biliary tract justifies outlining a system of treatment which would be on a rational basis. The pathogenesis is considered extensively from the standpoint of a metabolic disorder, infection and stasis in the biliary tract. The authors outline their plan of therapy for these disturbances, which emphasizes diet (low in cholesterol and fat), repeated duodenal drainage, the eradication of focal infection, the administration of vaccines, bacterial filtrates, cholagoges and cholagogues and the correction of constipation. A diet low in fat is usually advised, but if there is evidence of stasis in the biliary tract (determined by the results of duodenal intubation and cholecystography) fats are given to stimulate the function of the gallbladder. A chapter on jaundice by Cantarow outlines this complication adequately. A chapter is also devoted to the medical management of the patient with cholelithiasis.

It is difficult to understand the authors' enthusiasm for medical treatment, especially for drugs and vaccines and similar forms of therapy. Many will find it difficult to appreciate that a 465 page monograph could be developed pertaining to the medical treatment of cholecystitis and cholelithiasis. In general, the reviewer feels that he would hesitate to recommend this book.

**Manuel de coprologie clinique** By R. Goiffon. Third edition. Price, 28 francs. Pp 274, with 42 figures and 3 plates. Paris: Masson & Cie, 1935.

Goiffon's manual on the clinical study of the stools is divided into four parts. Part 1 is devoted to a brief introductory discussion of the normal physiology and digestion concerned in alimentation. This discussion, though inadequate from the physiologist's point of view, satisfactorily serves its purpose in a manual.

Part 2 includes a good presentation of the various forms of quantitative and qualitative analyses of the stool. The proper collection of a specimen and many other points that were formerly considered insignificant are described. More than one technic of analysis as well as the author's technic of preference is presented with the study of each factor. He thoroughly covers the subject of analysis of the stool, beginning with a discussion of its physical characteristics and including such subjects as macroscopic and microscopic material, chemical studies for its reaction, albuminous substances, blood, porphyrine, bile, phenols, indole, fats, ferments (such as catalase, trypsin, amylase and other digestive ferments), animal parasites, bacteria and many more factors which may be of interest to the clinician. Goiffon correlates the findings with normal and disturbed gastro-intestinal physiology and interprets them in terms of health and disease.

Part 3 is devoted to various disturbances in the gastro-intestinal function and to the changes in the stools that may be expected to be revealed on careful examination. Among the conditions discussed are gastric, biliary and pancreatic insufficiency, the colitides and motor dysfunction. He groups with each clinical syndrome the findings in the stool which are most often noted. He emphasizes the fact that the results of an examination of the stool are only an adjunct to the clinical picture, yet an important one.

Part 4 includes a brief review of the treatment of various gastro-intestinal disturbances which are responsible for changes in the stool. Goiffon makes no attempt to cover the entire subject of treatment in gastro-intestinal disease but does attempt to show how proper treatment is usually reflected in the stool by changes toward the normal.

The manual is well written, is very inclusive and is easily comprehended. Only occasionally does Goiffon refer to the literature, and therefore he gives only a short bibliography. The tables, illustrations and figures are good but too few. This manual is an excellent source of information on a subject which has been neglected in this country.

## CAN THE NEUROLOGIC COMPLICATIONS OF PERNICIOUS ANEMIA BE PREVENTED?

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NEW YORK

Nine years has elapsed since Minot and Murphy discovered the value of liver therapy for pernicious anemia. This period of time appears sufficiently long to allow a fair evaluation of the results achieved. But while this may hold true for the hematologic phase of the disease, there is considerable diversity of opinion concerning the neurologic aspects. This relates to two distinct questions: one is whether neurologic complications, once they have arisen, can be ameliorated or made to disappear by means of liver therapy, the other is whether adequate therapy can prevent the onset of neurologic complications in a patient not as yet affected.

In a previous study<sup>1</sup> I reported some observations bearing on the first problem. The findings indicated that in cases of advanced subacute combined degeneration treatment with liver had negligible effects. These findings appeared in conformity with what one would anticipate from a knowledge of the underlying pathologic condition in this stage of the disease—an irreparable destruction of the axis-cylinders. At the same time mention was made of the more auspicious reports of other investigators, for instance, Ungley and Suzman, Minot and Murphy and Richardson, and it was suggested that perhaps the earlier and more intensive application of treatment, at a time when irreversible changes in the nervous system had not yet occurred, accounted for the favorable results obtained.

The present study is concerned with the second question mentioned, namely, whether the neurologic complications of pernicious anemia can be prevented. The material for the previous study, coming as it did from the wards of a service for patients with chronic nervous diseases, could not be utilized for this purpose, since, obviously, only patients who already showed neurologic complications severe enough for them to seek hospitalization would be available. The opportunity to study a

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<sup>1</sup> Needles, W. Neurologic Complications of Pernicious Anemia, *Arch Neurol & Psychiat* 26:346 (Aug) 1931.

more suitable group was offered in the hematologic clinic of the Mount Sinai Hospital, where patients with earlier stages of the disease were encountered<sup>2</sup> There 30 consecutive and unselected cases of pernicious anemia were studied Some of these cases had to be excluded from consideration because of the presence of other etiologic factors capable of producing changes in the nervous system Thus, one patient had syphilis, another had shown neurologic signs immediately after the intraspinal injection of an anesthetic and a third had, in addition to anemia, diabetes mellitus, chronic alcoholism and hypertension

Another group of cases had to be eliminated because the liver therapy was inadequate, in some instances because the patient wilfully neglected the prescribed regimen (5 cases) or because what seemed to be an adequate and carefully supervised administration of liver did not produce the desired result, judging by the hematopoietic response (2 cases) One of these patients had to be readmitted to the hospital, and there signs of severe anemia were presented The other, though receiving maintenance doses of liver, repeatedly showed an unsatisfactory hemoglobin content, ranging from 49 to 65 per cent

In still another group of cases which were considered unsuitable there was evidence of neurologic involvement prior to the time when liver therapy was instituted (4 cases)

Finally, 2 cases in which signs of mild involvement of the spinal cord were present were not included, since they had not, before the beginning of therapy, been subjected to a detailed neurologic examination and preexistent neurologic signs had not been ruled out This may well happen if the patient is observed in the medical ward of a hospital, as usually happens, and does not present striking evidence of neurologic disease The more subtle deviations from the normal may then be overlooked

It is apparent that a considerable proportion of the cases originally studied had to be discarded But the criteria for exclusion cannot be regarded as too rigid if one agrees that in evaluating the effects of liver therapy one should deal with (1) patients whose neurologic status has been carefully checked before the institution of therapy and who have been found normal, (2) patients who are free from other conditions capable of producing neurologic signs and (3) patients who have faithfully adhered to the treatment and have received adequate doses of liver, as determined by the response of the blood Actually, consistent adherence to these criteria would have diminished the number of cases even more

Certain difficulties, which have doubtless confronted other investigators in this field, were encountered in the study of these cases Owing to the prolongation of life happily afforded by the use of liver, the

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2 Dr Nathan Rosenthal gave permission for the study of these cases

history has in many cases become a long one. The patients as a result are often uncertain and hazy about the vicissitudes of treatment, especially when the doses, the preparation and the route of administration have varied from time to time. For this reason also the treatment of one patient cannot readily be compared with that of another.

In addition, there is always the human factor to be dealt with, often thwarting the most assiduous attempts at accuracy. This was brought out strikingly, for example, in a patient who, despite apparently adequate therapy, had shown progression of the neurologic signs. When this patient, a rather proud and independent person, was questioned more closely, she admitted somewhat reluctantly that she had accepted the prescription for liver extract each time but that, not having the money to pay for the drug and not wishing to disclose her poverty, she had gone home without having the prescription filled. The records of the clinic indicated simply that the patient was receiving therapy regularly.

Another difficulty arises from the fact that since the disease not infrequently affects persons of advanced age, there may supervene, during the course of treatment, manifestations of neurologic disease not necessarily attributable to subacute combined degeneration. Arteriosclerotic changes may play a rôle, or the patient may manifest the "normal" alterations, notably of vibratory sensation, that the studies of Weisenburg have made familiar.

Cognizance has been taken of these various facts, and an attempt has been made to give them due consideration wherever necessary.

#### COMMENT

Of the 13 patients studied, the first showed minimal evidence of neurologic involvement eight and one-half years after the onset of symptoms, the second showed no involvement after eight and one-half years, the sixth showed no involvement after five and one-half years, the ninth showed no involvement after four and one-half years and the tenth showed no involvement after five and one-half years. The third patient showed slight signs of involvement of the pyramidal tracts seven and one-half years after the onset of the illness. The fourth patient, in whom the disease had run for nine years, showed merely vibratory disturbances over the lower half of the body. In both the last 2 cases there was no record of a detailed neurologic examination before liver therapy was instituted for purposes of comparison with the recent status. The fifth patient six years after the onset presented vibratory disturbances in the lower half of the body and moderate hyperreflexia. In view of the age of the patient and the presence of marked generalized vascular disease, even the few signs presented could not be attributed entirely to subacute combined degeneration. The seventh patient showed moderate hyperreflexia, a positive Babinski sign on

the left side, vibratory disturbances in the lower half of the body and disturbances of the position sense in the small toes of both feet six years after the onset of symptoms. However, the liver therapy was

*Data on Thirteen Patients with Pernicious Anemia*

Case	Duration of Symptoms Before Institution of Treatment	Duration of Treatment, Years	Neurologic Status Before Institution of Treatment	Present Neurologic Status	Comment
1	12 mo	8½	Normal	Hyperactive knee jerks, diminished vibration at toes	.
2	Short time (indefinite)	8½	Depression of deep reflexes	Normal	Brief omission of therapy
3	6 mo	7½	Detailed information lacking	Slight signs of involvement of pyramidal tracts	
4	8 mo	9	Detailed information lacking	Vibratory disturbances at and below iliac crests	
5	?	6	Detailed information lacking	Vibratory disturbances at and below iliac crests, moderate hyperreflexia	Aged 67, vascular disease
6	6 wk	5½	Normal	Normal	Brief omission of therapy
7	2 mo	6	Normal	Moderate hyperreflexia, Babinski sign on left, vibration diminished at and below iliac crests, loss of position sense at toes	Inadequate therapy, aged 66
8	?	4½	Normal	Vibration sense absent in left foot, diminished in right foot and fingers	
9	6 mo	4½	Detailed information lacking	Normal	Therapy inadequate at times
10	12 mo	5½	Normal	Normal	Occasional lapses of therapy
11	6 mo	4	Detailed information lacking	Minimal vibratory disturbances, hyperactive knee jerks	Aged 59, inadequate therapy at times
12	18 mo	6½	Weakness of legs, loss of vibration sense at and below ilium	Hyperreflexia, vibration as before, loss of position sense in toes	
13	2 yr	8½	Upper reflexes diminished, loss of ankle and knee jerks, ataxia of upper limbs, vibratory disturbances	Reflexes of upper extremities depressed, vibration sense disturbed in all limbs	

not optimal in this case. The eighth patient showed merely vibratory disturbances in the hands and feet after at least four and one-half years of illness. The eleventh patient after four years of illness showed minimal vibratory disturbances in the hands and feet and hyperactive patellar and suprapatellar reflexes. However in a person aged 59 these findings are not so definitely indicative of subacute combined degenera-

tion as they would be in a younger person. In addition, lapses of therapy occurred in this case. The last 2 patients, who presented some evidence of neurologic involvement before they were given liver therapy six and one-half and eight and one-half years, respectively, after the onset of symptoms, showed no significant progression of the involvement.

The salient features in these 13 cases are shown in the accompanying table.

One fact that stands out significantly in this study is the relatively short period for which each patient was ill before the diagnosis of pernicious anemia was established and appropriate therapy was instituted, and brings out clearly the necessity for early diagnosis and treatment.

When one considers the usual course of pernicious anemia and subacute combined degeneration before liver therapy was introduced, the results obtained at present can be better appreciated. Even after the development of paresthesias in the limbs has been ruled out as sufficient evidence of involvement of the spinal cord, estimates of the frequency of disease of the spinal cord in pernicious anemia vary from 40 per cent (Suzman) to 80 per cent (Woltman). Cabot reported lesions of the spinal cord in 84 per cent (82 cases) of those examined histologically. Presumably, the longer the illness lasts before treatment is instituted, the greater the probability that spinal complications will supervene, so that in a group of patients with such an unusually long duration of symptoms as was noted here the incidence of involvement of the spinal cord would have been high. Yet, some of these patients have already been ill for from four to eight and one-half years without any evidence of involvement of the spinal cord, and some have been ill for an equal period of time with only minimal or mild involvement. The average duration of the illness for the patients who are still alive and well is six and one-half years, a period exceeding by far not merely the time usually required for the development of a severe pathologic condition of the spinal cord but the customary duration of the entire illness before the advent of liver therapy. For, according to Cabot,<sup>3</sup> in his study based on 1,200 cases of pernicious anemia, 556 of 699 deaths occurred within three years and 628 within four years.

It has been noted in several instances (cases 2, 6, 7, 9, 10 and 11) that therapy was not entirely satisfactory, either because the patient disregarded medical advice or because what was regarded as a maintenance dose of liver did not evoke a satisfactory response as judged by the blood picture. It may at first glance appear illogical, on the one hand,

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3 Cabot, R. C., in Osler, W., and McCrae, T. *Modern Medicine*. Philadelphia, Lea & Febiger, 1915, vol. 4.

to attribute the appearance of signs in one group of patients to the inadequacy of therapy and then to point out that some of the patients remained entirely or almost entirely free from neurologic complications despite lapses in therapy. This seeming paradox is resolved on closer analysis, however, for while one must agree that a patient who was not adequately treated and subsequently showed signs of involvement of the spinal cord might conceivably have shown a similar course with adequate therapy—such has been the experience of numerous observers, as well as mine—nevertheless there is no justification for assuming that this is true in all cases. The present study illustrates this. On the other hand, as regards the patients who fared well despite certain lapses in therapy, one must conclude that the amount of liver which these patients received was adequate to tide them over the periods when they abstained from liver. It cannot be denied that without liver therapy these patients would have shown imposing signs of myelopathy and would have succumbed in a much shorter time than they have survived, neurologically intact, thus far. The impression is gained that there is variability in the individual resistance to disease of the spinal cord and that one person may require a smaller maintenance dose of liver than another to keep the nervous system intact.

In the literature one finds as little unanimity of opinion regarding the preventive value of liver in subacute combined degeneration of the spinal cord as one does regarding its curative value, once signs of involvement of the spinal cord have set in. In the previous study the divergent views of Minot and Murphy, Lottig, and Witzleben and Ungley and Suzman, on the one hand, and of Curschmann and Redlich, on the other, were cited. Reference to more recent studies shows that this divergence of opinion still exists. Thus, Starr<sup>4</sup> reported on 8 cases of pernicious anemia. In 4 patients who were considered to have received adequate treatment, there was no progression in the neurologic signs, but in 4 who were considered to have received inadequate treatment, 2 of whom had serious infection of the bladder, such progression did occur. Christoffersen<sup>5</sup> reported on 24 patients with pernicious anemia who were treated for from one to four years. Twelve of these patients remained free from neurologic involvement. Four showed evidence of neurologic involvement before therapy was instituted. Of the 8 patients in whom signs developed during the course of treatment, only 1 was considered as having been adequately treated. Meulengracht<sup>6</sup> reported on 17 patients who showed improvement after liver

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4 Starr, P. The Prevention of Spinal Cord Degeneration in Pernicious Anemia, *J A M A* **96** 1219 (April 11) 1931

5 Christoffersen, N. R. Anamische Myelopathien bei Leberbehandlung, *Acta med Scandinav*, supp 50, 1932, p 395

6 Meulengracht, E. Verhütung und Behandlung der Rückenmarksstörungen bei perniziöser Anämie, *Klin Wchnschr* **12** 1163 (July 29) 1933

extract was replaced by stomach preparations. He expressed the opinion that most of the patients in whom myelopathy developed after treatment had been instituted were doubtless underdosed, since they improved when stomach preparations were substituted. In a discussion before the Royal Society of Medicine Witts<sup>7</sup> mentioned the experiences of Wilkinson, who treated 264 patients with pernicious anemia for periods ranging up to three and one-half years without the development of neurologic signs. All were treated with preparations of stomach orally. Seyderhelm,<sup>8</sup> on the other hand, reported that of 53 patients who died of pernicious anemia, signs of involvement of the spinal cord developed in 7 despite therapy, of 40 living patients, 4 showed the development of signs despite therapy. He found that the patients who escaped spinal complications were those who showed especially high red blood cell counts during remissions. Garvey, Levin and Guller<sup>9</sup> found that of 19 patients who originally showed no neurologic involvement, 9 had been satisfactorily treated, and in only 1 did signs of involvement of the spinal cord develop, while of 10 unsatisfactorily treated patients, 5 became neurologically affected. Grinker and Kandel<sup>10</sup> studied a fairly large series of cases and concluded that "liver therapy is not efficacious in improving or preventing degeneration in the central nervous system complicating pernicious anemia." Analysis of their cases, however, shows that only 2 patients (cases 20 and 27) were neurologically intact before treatment was instituted and that signs developed subsequent to treatment. There is little ground, therefore, for their generalization as to the preventive value of liver therapy. Finally, Goldhamer, Bethell, Isaacs and Sturgis,<sup>11</sup> in their series of 461 patients, found 18 who were neurologically normal at the original examination. In 8 of these patients spinal complications developed, while in 9 they did not. One patient could not be followed.

In the light of these facts it is obvious that at present it is impossible to formulate any hard and fast rule regarding the preventive value of liver. In some cases liver therapy prevents the onset of myelopathy, in others it does not.

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7 Witts, L. J., in Discussion on the Treatment of Subacute Combined Degeneration, *Proc Roy Soc Med* **27** 787 (April) 1934.

8 Seyderhelm, R. Sieben Jahre Lebertherapie, *Deutsche med Wchnschr* **59** 1193 (Aug 4) 1933.

9 Garvey, P. H., Levin, P. M., and Guller, E. I. Effect of Liver Therapy on the Neurologic Aspects of Pernicious Anemia, *Ann Int Med* **6** 1441, 1933.

10 Grinker, R. R., and Kandel, E. Pernicious Anemia. Results of Treatment of the Neurologic Complications, *Arch Int Med* **54** 851 (Dec) 1934.

11 Goldhamer, S. M., Bethell, F. H., Isaacs, R., and Sturgis, C. C. The Occurrence and Treatment of Neurologic Changes in Pernicious Anemia, *J A M A* **103** 1663 (Dec 1) 1934.



Of the patients who formed the basis for this study, it so happened that none who received sufficient treatment showed more than insignificant neurologic signs—and then, in several cases not definitely attributable to subacute combined degeneration—while 4 showed no signs whatever. The cases were thought to be especially informative because of the long duration of the illness. The reason for the different responses in different patients is still unknown. It may ultimately be found to rest on variations in the constitutional make-up. Before this impression is established as a fact, however, it will be necessary to study a large group of patients at approximately the same stage of the disease and treated with equal doses of the same preparation of liver. In other words, it will be necessary to rule out the possibility that one type of preparation may be more potent than another in combating the myelopathic process in pernicious anemia.

The present series of cases, at any rate, renders one a little more optimistic about the chances of obtaining gratifying results and indicates that the attitude of therapeutic nihilism that exists in certain quarters is not justified. The development of subacute combined degeneration certainly must not be regarded as inevitable. If any added stimulus is needed at this late date for prompt and energetic treatment of pernicious anemia, the present findings provide it.

The detailed report of the cases is given in the reprints of this article.

# POSTURAL HYPOTENSION

WITH PARTICULAR REFERENCE TO ITS OCCURRENCE IN DISEASE  
OF THE CENTRAL NERVOUS SYSTEM

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AND

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Normally, the arterial blood pressure in man is maintained relatively stable in spite of marked variations in body posture. Failure of this postural adaptation occasionally occurs, with the production of symptoms which may handicap the patient severely. Bradbury and Eggleston<sup>1</sup> first described the clinical syndrome of "postural hypotension" in 1925. Since that time a total of twenty-six definite case reports have appeared in the literature,<sup>2</sup> including reports of cases in which the hypotension

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From the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard) of the Boston City Hospital and the Department of Medicine of Harvard Medical School

1 Bradbury, S, and Eggleston, C Postural Hypotension A Report of Three Cases, *Am Heart J* **1** 73, 1925

2 (a) Ghrist, D G, and Brown, G E Postural Hypotension with Syncope Its Successful Treatment with Ephedrin, *Am J M Sc* **175** 336, 1928 (b) Asworth, O O Postural Hypotension A Report of Two Cases, *Virginia M Monthly* **56** 260, 1929 (c) Riecker, H H, and Upjohn, E G Postural Hypotension, *Am Heart J* **6** 225, 1930 (d) Schellong, F Störung der Kreislaufregulation, eine neues Symptom bei Insuffizienz des Hypophysenvorderlappens, *Klin Wchnschr* **10** 100, 1931 (e) Strisower, R Ueber bedeutende Blutdrucksenkung nach Arbeit und bei Aenderung der Körperlage bei Tabes dorsalis, *Ztschr f klin Med* **117** 384, 1931 (f) Barker, N W, and Coleman, J H Postural Hypotension Associated with Arteriosclerosis, *M Clin North America* **15** 241, 1931 (g) Sanders, A O Postural Hypotension A Case Report, *Am J M Sc* **182** 217, 1931 (h) Duggan, L B, and Barr, D P Postural Hypotension Occurring in a Negro with Addison's Disease, *Endocrinology* **15** 531, 1931 (i) Laubry, C, and Doumer, E L'hypotension orthostatique, *Presse med* **40** 17, 1932 (j) Sanders, A O Postural Hypotension with Tachycardia A Case Report, *Am Heart J* **7** 808, 1932 (k) Lian, C, and Blondel, A L'hypotension arterielle orthostatique, *Paris med* **1** 179, 1933 (l) Barker, N W Postural Hypotension Report of a Case and Review of the Literature, *M Clin North America* **16** 1301, 1933 (m) Allen, E V, and Magee, H R Orthostatic (Postural) Hypotension with Syncope, *ibid* **18** 585, 1934 (n) Gainshorn, J A, and Horton, B J Postural Hypotension Report of a Case, *Proc Staff Meet, Mayo Clin* **9** 541, 1934 (o) Weis, C R Postural Hypotension with Syncope Report of a Case Cured with Ephedrine Sulfate, *Ann Int Med* **8** 920, 1935 (p) Croll, W F, Duthrie, R J, and MacWilliam, J A Postural Hypotension Report of a Case, *Lancet* **1** 194 (Jan 26) 1935

occurred in association with tabes dorsalis and Addison's disease. It is questionable whether certain additional cases reported should be included in the total number. Schellong<sup>2a</sup> cited five cases of postural hypotension but gave insufficient data on three to warrant their inclusion. In two of the cases reported by Laubry and Doumer<sup>21</sup> (cases 3 and 5) the fall in blood pressure was so slight, inconstant and transitory that, as Barker<sup>21</sup> suggested, it seems unjustifiable to class these cases among those of this syndrome. The same objection holds for the cases reported by Tripodi<sup>3</sup> and by Rudsit<sup>4</sup>. It therefore appears that this condition is either of rare occurrence or is relatively seldom recognized. It is our belief that it is not uncommon, although patients with severe and dramatic symptoms are probably not frequently encountered. In the past two and one-half years we have seen six patients with postural hypotension at the Boston City Hospital.

In their original description of postural hypotension Bradbury and Eggleston<sup>1</sup> tabulated seven characteristics of the condition. These were (1) a syncopal attack when the patient stood, with a marked drop in the systolic blood pressure, (2) a slow and unchanging pulse rate, (3) anhidrosis, (4) increased distress during the heat of summer, (5) a slightly low basal metabolic rate, (6) signs of slight and indefinite changes in the central nervous system and (7) a blood urea content at the upper limit of normal. In addition, they frequently encountered (1) a greater output of urine at night than during the day, (2) impotence, (3) a false appearance of youth, (4) pallor and (5) secondary anemia. In the cases cited in subsequent reports all of these characteristics have not been shown, which is not surprising since the original report was based on an analysis of only three cases. It now appears justifiable to define the syndrome of postural hypotension, as has Barker,<sup>21</sup> as one in which there is an immediate, persistent and marked fall in the systolic blood pressure when the patient stands and a similar but somewhat smaller drop in the diastolic blood pressure, frequently accompanied with dizziness, fainting and other symptoms. The drop in the systolic pressure in each case should be frequently but not necessarily invariably as great as 50 mm of mercury. Partial or complete anhidrosis is of frequent occurrence. A heart rate which either is absolutely unchanged or fails to increase to a normal degree when the patient stands is also commonly seen, particularly in the cases of severe involvement.

The following report concerns the clinical observations made on six patients with postural hypotension, on two of whom a detailed physio-

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3 Tripodi, M. L'ipotensione arteriosa ortostatica, Policlínico (sez. prat.) **39** 797, 1932.

4 Rudsit, K. Zur Behandlung vasoneurotischer Störungen mit Hypophysenvorderlappenpräparaten mit besonderer Rücksicht auf die Blutdruckreaktion bei Aenderung der Körperlage, Wien klin. Wchnschr. **47** 878, 1934.

logic investigation was carried out concerning the mechanism of the disturbance

*CASE 1—Clinical History*—H H, a 57 year old married man, a locksmith, entered the neurologic service of the Boston City Hospital on July 22, 1932, complaining of weakness. For six months he had had generalized abdominal soreness which was relieved by pressure, anorexia, gas, alternating constipation and looseness of the bowels and impotence. He had lost 34 pounds (15.5 Kg) in the past year. For four weeks he had suffered from increasing weakness and dizziness on standing. Twice he had fainted when getting out of bed.

The family, marital and past histories were noncontributory.

*Physical Examination*—The patient was pale and had an anxious expression. He appeared older than his age and gave evidence of having lost weight. The legs showed marked varicose veins. There was no definitely abnormal pigmentation. Neurologic examination showed no pupillary abnormality, there was slight rotatory nystagmus on the left and some impairment of hearing. Postural hypotension was present, as will be discussed later.

*Laboratory Findings*—Repeated examination of the urine showed the presence of albumin in amounts varying from moderate to large. The specific gravity was fixed at from 1.010 to 1.012. The centrifugated sediment showed an occasional leukocyte and granular cast. The blood was normal as to the hemoglobin and the number of red and white corpuscles. The Kahn test of the blood was negative. The nonprotein nitrogen content of the blood was normal, ranging about 30 mg per hundred cubic centimeters until two days before the patient died, when it rose to 175 mg. The blood sugar content during fasting was 80 mg. No occult blood was present in the stool. Gastric analysis showed normal amounts of free hydrochloric acid after an alcohol test meal. Rentgenograms of the gastrointestinal tract gave negative results.

A diagnosis of postural hypotension was made, but no underlying organic disease could be demonstrated, with the exception of evidence of some renal damage. Addison's disease was seriously considered, but not enough confirmatory evidence existed to make the diagnosis definite.

*Course*—Treatment was of no avail. Ephedrine in doses of  $\frac{3}{4}$  grain (0.05 Gm) three times daily, epinephrine and extract of adrenal cortex gave no relief. Atropine made the patient feel weaker.

The patient's condition gradually grew worse. The weakness increased, and attacks of syncope became more frequent. On November 14 slight fever developed for the first time. The patient became markedly weaker, but no new symptoms developed. He died quietly in his sleep on November 21.

*Autopsy*—The relevant autopsy observations were as follows. The heart was essentially normal in size, weighing 380 Gm. The myocardium was pale and flabby. There was marked sclerosis of the coronary arteries, but the lumens of these vessels were everywhere patent. The aorta showed moderate atheromatous changes and scarring, there was slight atheroma of the cerebral vessels. The carotid sinuses, unfortunately, were not examined. The lungs showed chronic passive congestion and an early stage of bronchopneumonia. The adrenal glands were grossly normal, but microscopic examination revealed an extensive deposit of pink-staining hyaline material, chiefly in the middle zone of the cortex, with marked atrophy of the cellular elements due to pressure. There was moderate central congestion of the liver, with an acute hydropic degeneration of the center of the lobules and portal lymphocytic infiltration. The kidneys were

enlarged, weighing together 620 Gm. There was extensive destruction of the cortex, with infiltration by large numbers of leukocytes and the formation of multiple small abscesses. The glomeruli in the affected area were relatively well preserved. There was moderate hyalinization of small vessels. In the spleen there was a moderate amount of hyaline material, partly replacing the germinal centers. There was cerebral edema, but the brain was otherwise grossly and microscopically normal except for a cyst of the left choroid plexus, 2 by 1 by 1 cm. The spinal cord was not examined.

*Pathologic Diagnosis*—The diagnosis was an early stage of bronchopneumonia and pulmonary edema, acute hydropic degeneration of the liver, infectious nephritis—due to *Streptococcus haemolyticus* and *Bacillus coli-communis*, amyloidosis of the adrenal glands and spleen, cerebral edema and cyst of the choroid plexus.

*CASE 2—Clinical History*—M. T., an American housewife aged 69, entered the Boston City Hospital on June 6, 1934, complaining of weakness and attacks of dizziness on standing which had been noted for nine months. The dizziness, which had been progressive, consisted essentially of an "all gone" feeling, with blurring of vision but no rotatory vertigo. The patient had never completely lost consciousness but had repeatedly been forced to lie down to prevent what she was sure would have been complete unconsciousness, and on several occasions she had actually collapsed. In a recumbent position she felt well.

For fourteen years she had suffered from diabetes mellitus, which was well controlled by diet and about 20 units of insulin daily.

For the past year the patient had not noticed any sweating, even in warm weather, and for about two and one-half years she had suffered from increasing paresthesia and some numbness of the lower portion of the legs and feet and to some extent of the hands. She had always been constipated.

The family, marital and past histories were noncontributory.

*Physical Examination*—The patient was pallid and had a pasty complexion. She looked somewhat young for her age. The pupils were of normal size, equal and regular. They reacted to light and in accommodation. The heart was slightly enlarged, with a moderately loud systolic murmur, maximal in the pulmonic area, and an accentuated aortic second sound. The rhythm was regular at a rate of 72. The brachial and radial arteries were somewhat thickened. With the patient recumbent the arterial blood pressure was somewhat elevated, and there was postural hypotension. The lungs and abdomen were normal. There was moderate varicosity of the veins in both legs. Neurologic examination showed hyperactive but equal deep reflexes, except for the ankle jerks, which were absent. The vibration sense was absent in both legs, and the sense of position was slightly impaired in the feet.

*Laboratory Findings*—The urine was normal except for an occasional trace of sugar. The red blood cell count was 4,700,000, and the hemoglobin value, 81 per cent. The stained smear showed normal red and white blood cells. There was complete gastric anacidity, even after the administration of histamine. The nonprotein nitrogen content was 34 mg. per hundred cubic centimeters of blood. The basal metabolic rate was minus 13 per cent. The Kahn test of the blood gave a negative result.

A diagnosis was made of diabetes mellitus, mild arterial hypertension, mild generalized arteriosclerosis, postural hypotension and possibly beginning combined system disease.

*Course*—The course during the patient's stay in the hospital was uneventful. Her condition was extensively studied, as will be described later. She was dis-

charged on July 11. The dizziness was adequately controlled by 25 mg of ephedrine sulfate by mouth three times daily, but the symptoms of weakness continued. She was given in addition  $\frac{1}{2}$  grain (0.03 Gm) of thyroid daily and biweekly injections of 10 cc of liver extract. On September 2 she suffered a mild attack of coronary thrombosis and reentered the hospital on September 9. Recovery was uneventful, and the patient was discharged on November 2. The condition has remained essentially unchanged.

*CASE 3—Clinical History*—P. P., a French-Canadian newspaperman aged 46 and single, had been followed by the neurologic service of the Boston City Hospital for four years. In 1925 he burned his right hand severely, apparently because of a loss of temperature sensation. Shortly thereafter he noticed diplopia, hoarseness and numbness and weakness of the right hand and arm and later of the left hand and both legs. The symptoms had progressed until about four years before the present studies were made, since which time there had been little change. For seven years he had had practically no sweating. Occasionally during the past three or four years he had noticed some dizziness and blurring of vision when erect, but this symptom had been intermittent and never severe, and there had been no fainting. Otherwise the history was unimportant.

*Physical Examination*—With the exception of the neurologic findings and the postural hypotension, the results of physical examination were normal. The patient had a florid complexion even when erect. Neurologic examination on April 21, 1935, revealed rotatory nystagmus. The right pupil was larger than the left, and both pupils reacted poorly in accommodation but well to light. There was some hoarseness. Movement of the palate was diminished on the left, and the tongue was deviated to the left. The biceps reflex was absent on the right, and the radial and abdominal reflexes also were absent. The cremasteric reflex was diminished on the left. Bilateral Babinski and Chaddock reflexes were noted. There was absence of pain sensation over the face, and the temperature sense was absent over the head and shoulders as far as the level of the fifth cervical vertebra. There was a diminished sense of touch over the head and the lateral aspects of both arms. The sternocleidomastoid, trapezius and interosseus muscles were atrophied. There was slight weakness of both arms and the left leg and slight spasticity of the right leg. Past pointing and an intention tremor were noted in the right hand, with impairment of skilled actions. Bilateral adiadokokinesis, a tendency to fall toward the left and some ataxia were noted. A pilomotor test revealed no abnormality.

*Laboratory Findings*—Examination of the urine and spinal fluid and the red and white blood cell counts gave normal results. The Kahn reaction of the blood gave a negative result. The basal metabolic rate was minus 10 per cent.

*Diagnosis*—The diagnosis was syringomyelia and postural hypotension.

*CASE 4—Clinical History*—G. B., a single, unemployed Negro aged 69 years, was seen in the neurologic outpatient clinic of the Boston City Hospital on May 5, 1933, at which time a diagnosis of tabes was made. Lumbar puncture showed results consistent with an inactive lesion. The patient was unable to state the time of the appearance of the original syphilitic lesion. For ten years he had had lightning pains in the legs. There were no other tabetic symptoms. The patient had never perspired much and for the past eight or ten years practically not at all. Until two weeks before the studies were made, on July 31, 1934, he had never noticed dizziness, since then he had had several attacks while walking. There had been no gastro-intestinal disturbance or nocturia. Otherwise the history was irrelevant.

*Physical Examination*—On July 31, 1934, examination revealed no abnormality except for the neurologic findings and evidence of postural hypotension. The patient looked young for his age. The pupils were small, irregular, slightly unequal and fixed to light and reacted sluggishly in accommodation. The knee and ankle jerks were absent, and the position and vibration senses in the legs were impaired.

*Diagnosis*—The diagnosis was tabes dorsalis and postural hypotension.

*CASE 5—Clinical History*—M. L., a Jewish housewife aged 44, entered the Thorndike Ward of the Boston City Hospital on Nov. 27, 1934, with a complaint of nausea and vomiting for thirteen years. The gallbladder had been removed one year prior to the patient's present admission to the hospital, following which she was free from gastric symptoms for six months. Then the symptoms returned and were for the first time accompanied with cramps. For thirteen years she had been under treatment for tabes. For several years she had had shooting pains in the legs.

For a number of years she had been troubled with attacks of dizziness, which frequently continued until she fainted. These occurred when she assumed an upright position, usually in the morning. Lying down relieved the symptoms.

The family, marital and past histories were noncontributory.

*Physical Examination*—The patient looked healthy. There was no abnormality except for the neurologic signs and postural hypotension. The pupils were small and irregular, the left one being smaller than the right. Both reacted in accommodation but not to light. The knee and ankle jerks were absent. Sensation to touch and the vibration sense were diminished in both legs and feet.

*Laboratory Findings*—Examination of the urine and blood and roentgenograms of the gastro-intestinal tract revealed no abnormality. The Kahn reaction of the blood gave a weakly positive result. The spinal fluid showed 12 lymphocytes, a weakly positive Kahn reaction and a colloidal gold curve of 0011211000.

*Diagnosis*—The diagnosis was tabes dorsalis, ? gastric crisis, ? gastric neurosis and postural hypotension.

*CASE 6—Clinical History*—R. H., an American clerk aged 32 years and single, was admitted to the neurologic service of the Boston City Hospital on April 22, 1934. He had fallen from a third story window onto the pavement. He was picked up unconscious and brought to the hospital. By the time of admission to the hospital he had regained consciousness but was in profound shock, from which he rallied somewhat in about four hours. His previous history was unimportant.

*Physical Examination*—The abnormal physical findings were confined to the nervous system, with the exception of a few minor abrasions. There was complete loss of sensation from the level of the second dorsal segment down, and a partial sensory loss was noted in the first and second dorsal segments. The reflexes in the arm were present but much reduced. The patient could move the arms only slightly and suffered considerable pain in them. There was complete motor paralysis of the trunk and lower extremities, and the reflexes were absent.

Lumbar puncture showed no signs of block, the spinal fluid was slightly bloody. Roentgenograms of the spine revealed a fracture of the sixth cervical vertebra.

*Course*—The reflexes of the lower extremities had returned by May 20, 1935, and a mass reflex was present. Automatic function of the bladder and anal sphincters was attained at the same time. Moderate sweating of the paralyzed part of the body and an increased pilomotor response also appeared. Decubitus

ulcers developed, but by June 1935 they were largely healed. The pain in the arms had disappeared, and the strength of the arms was increased somewhat. Otherwise he remained in essentially the same condition. By Dec 25, 1934, however, there had been a slight return of sensation over the chest, and by June 2, 1935, he had slight sensory perception to the knees. The motor function remained entirely lost. After June 1934 he was able to sit in a reclining position at an angle of approximately 30 degrees in a wheel chair for two and one-half hours. There was some dizziness when he was first being propped up, but this gradually passed off. On some occasions, however, the dizziness was sufficiently marked to prevent his sitting at all. The vascular reactions were studied in June 1935.

*Diagnosis*—The diagnosis was hematomyelia.

TABLE 1—*Effect of an Erect Position and of Exercise on the Arterial Blood Pressure and on the Heart Rate*

Case	Arterial Blood Pressure, Mm of Mercury			Heart Rate			Symptoms When Erect	Etiology
	Reeumbent, Average and Range	Erect, Average and Range	Change Immedi- ately After Ever else	Reeum- bent, Average and Range	Erect, Average and Range	Change Immedi- ately After Ever else		
1	120/84	65/52	+10/+10	86	92		Feeling of faintness to absolute syncope	? ?? Addison's disease
2	154/80 110 190/60 100	91/62 62 135/46 86	-22/-16	73 70-84	75 75 86	+17	Dizziness, blurring of vision "all gone" feeling	?
3	121/82 96 136/64 90	58/44 33 80/26 60	+42/+24	68 62 80	82 72-90	-6	Dizziness, buzzing in ears, blurring of vision	Syringo myelia
4	129/69 115 140/60 78	81/48 62 110/41 56	+32/+8	75 70 80	83 82 86	+12	Occasional dizziness	Tabes dorsalis
5	125/81 120 135/76 85	82/60 75 95/56 65	+2/0	104 100 110	110 106 114	0	Occasional dizziness	Tabes dorsalis
6	86 68 98/74	56/44 42/30		95 70	105 103		Marked dizziness* Marked dizziness†	Hemato myelia

\* Aug 20, 1934, tilted to 40 degrees only

† July 1, 1935, tilted to 60 degrees only

#### INVESTIGATIVE PROCEDURES

*Postural Hypotension*—Each patient showed an immediate, profound and persistent drop in the arterial blood pressure when in the erect position (table 1). The extent of the drop varied from time to time, frequently without detectable cause, although it was often worse on warm days. A marked drop was observed with least regularity in case 5, although on several occasions it exceeded 50 mm of mercury. The drop in the blood pressure was the same whether the change of position was effected passively on a tilting table or actively by having



the patient stand. The development of dizziness in a given patient bore a rough relationship to the level of the blood pressure when he was erect, although this relationship was neither exact nor consistent. There was no correlation among the patients as to the level at which the symptoms developed.

The second patient showed no significant change in the heart rate when she stood. The fifth patient persistently had a pulse rate of from 100 to 120 regardless of her position. The remaining patients showed a rise in the heart rate when they stood, but it was less than one would expect as a compensation for the lowered blood pressure.

*Exercise*—It has been noted previously<sup>5</sup> in cases of postural hypotension that immediately, after a walking exercise the blood pressure may decrease and the patient's symptoms may increase. This was found to be true in case 2 but not in cases 1, 3, 4 and 5 (table 1). Schellong<sup>2d</sup> has also observed that exercise of the legs when the patient is recumbent produces a lowering of the arterial pressure. We were unable to confirm this observation in the three patients studied in this regard (cases 2 to 4), all of whom showed a slight rise in pressure.

*Emotion*—It was noted that the patients, particularly the second patient, tended to show considerable fluctuations in blood pressure from day to day and that in cases 2 to 5 the blood pressure apparently rose under emotional stress. Unfortunately, the vascular reflexes of the first patient were not tested.

*Pain*—In case 3 the application of an uncomfortably tight pressure cuff to the arm on one occasion produced an increase in the blood pressure with the patient recumbent and a lessening of the drop when the patient stood, but when the test was repeated there was no effect. Cuffs about the ankles, similarly, were without effect. In cases 2 and 4 no change was produced by tight cuffs about the arm.

It has been shown<sup>6</sup> that normally a sensory stimulus, such as pinching the skin of the arm, produces a definite and immediate decrease in the blood flow through that extremity. In the second patient, this reaction was entirely absent, although in the third patient it was normal. In the sixth patient the reaction was present, although its onset was delayed. The so-called galvanic reflex is a decrease of the cutaneous resistance, which also occurs as a result of a stimulus such as pinching.<sup>7</sup> This was normal in the third patient but absent in the second and sixth patients. It is of interest that it was absent in the patient with

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5 Schellong<sup>2d</sup> Strisower<sup>2e</sup>

6 Capps, R. B. To be published.

7 Solomon, P. The Psychogalvanic Reflex. Applications to Neurology and Psychiatry, Arch. Neurol. & Psychiat. 34:818 (Oct.) 1935.

transection of the spinal cord, since it has been shown<sup>8</sup> that in animals with experimental transection of the spinal cord, although there is a latent period of weeks during which the reflex is absent, it eventually returns

*Reflex Vasodilatation to Heat*—In cases 2 and 3 the blood flow in the hand was measured after one leg had been heated. Normal reflex vasodilatation was produced by this method in both patients. This test corresponds to that described by Gibbon and Landis,<sup>9</sup> who found that a reflex rise in the temperature of the skin was due to sympathetic impulses arising in the brain as a result of the stimulus of the warmed blood. In case 3 the effect of a change in posture was studied after one arm had been immersed in water at a temperature of 42 C. It was found that the drop in pressure and dizziness with the patient erect were greater than during a control observation.

*Cold*—Immersion of the arm of this patient in ice-water increased the blood pressure with the patient recumbent from 100 systolic and 65

TABLE 2—*Effect of Pressure on the Carotid Sinus*

Case	Fall in Blood Pressure, Mm. of Mercury	Fall in Pulse Rate	Symptoms
1	6	0	0
2	10-42	Slight	0
3	0	0	0
4	20-25	0	0
5	14-54	Very slight	Dizziness
6	0	Slight	Slight dizziness

diastolic to 120 systolic and 80 diastolic, but it was without effect in lessening the drop when he stood. Gainshorn and Horton<sup>2n</sup> found in studying one patient with orthostatic hypotension by this procedure that the pressure was increased with the patient recumbent and did not fall to as low a level when he was standing.

It is therefore apparent that the vascular reactions and certain at least of the vasomotor reflexes were maintained in the patients studied.

*Carotid Sinus Reflex*—This reflex was studied in all patients, and the results are shown in table 2.

The fifth patient had a mildly hyperactive carotid sinus reaction, and the others had normal reactions. In only one, the patient with syringomyelia, was no effect produced. The two patients (cases 2 and 3) to whom sodium cyanide was administered intravenously for mea-

8 Richter, C. P. Galvanic Skin Reflex from Animals with Complete Transection of the Spinal Cord, *Am J Physiol* **93** 468, 1930.

9 Gibbon, J. H., Jr., and Landis, E. M. Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, *J Clin Investigation* **11** 1019, 1932.

surement of the circulatory time showed a normal respiratory response to the drug. It is known that sodium cyanide acts on the carotid sinus<sup>10</sup>. This is the only evidence available that the carotid sinuses of patients with postural hypotension react normally to internal stimulation.

*Restriction of the Circulation to the Legs*—The effect of eliminating the circulation through the legs was studied in cases 2 to 4 by means of blood pressure cuffs around both thighs inflated until there was a pressure of 250 mm. of mercury.

In each case the drop in pressure was partially abolished. This was largely, if not entirely, due to the mechanical exclusion of the circulation in the legs, which removed an appreciable portion of the vascular bed involved in the disturbance in the postural reflex. That it was not caused by a vasoconstricting reflex resulting from the discomfort of the cuff on the thighs is indicated by the fact that cuffs around the ankles or one arm, with the one exception previously discussed, which were equally uncomfortable, failed to prevent the full

TABLE 3—*Effect of Occluding the Circulation to the Legs*

Case	Blood Pressure, Recumbent		Blood Pressure, Erect		Symptoms, Erect	
	Without Cuff	With Cuff	Without Cuff	With Cuff	Without Cuff	With Cuff
2	148/80	156/84	60/50	90/62	Dizziness	0
3	118/80	134/96	66/46	114/84	Dizziness	0
4	126/70	124/70	88/56	110/61	0	0

drop in blood pressure, regardless of whether the blood pressure with the patient recumbent was somewhat elevated by the procedure.

These observations are in agreement with those of Allen and Magee<sup>2m</sup> but not with those of Ghrist and Brown,<sup>2n</sup> who noted no effect from this procedure. Our observations indicate that disturbance of the normal postural reflex is widespread, including the vessels of the lower extremities as well as those of the splanchnic area.

In case 1 tight bandaging of the legs reduced the dizziness when the patient stood, although it did not significantly change the drop in blood pressure. A similar effect in one case was observed by Bradbury and Eggleston.<sup>1</sup>

*Effect of an Abdominal Binder*—The application of a tight abdominal binder also was effective in lessening the drop in blood pressure and the amount of dizziness in two of three patients.

10 Heymans, C., Bouckaert, J. J., and Dautrebande, L. Sinus carotidien et reflexes respiratoires. III. Sensibilite des sinus carotidiens aux substances chimiques, action stimulante respiratoire reflexe du sulfure de sodium, du cyanure de potassium, de la nicotine et de la lobeline, Arch. internat. de pharmacodyn. et de therap. 40: 54, 1931.

*Dynamics of the Circulation (Table 5)*—Physiologic measurements of the hemodynamics were carried out with the subject on a tilting table, first recumbent and again after having been tilted to an angle of 75 degrees for at least ten minutes. The total blood flow was well maintained with the subject in the erect position. The decreases in cardiac output which were noted were no greater than those that are frequently found in normal subjects by the same method, particularly in those with poor postural adaptation.<sup>11</sup> Lian and Blondel<sup>2b</sup> found an increase in the cardiac output of one patient from 4 liters a minute recumbent to 12 liters when erect, a change which they attributed to increased muscular activity when he was erect. Since they gave no details regarding the method employed, this extraordinary finding can hardly be accepted. As regards the circulation time, Bock, Dill and Edwards,<sup>12</sup> using the histamine method, found the arm to face time of normal subjects essentially the same in the standing as in the lying position. Schellong and Heinemeier<sup>11b</sup> found that in patients with good adaptation the circulation time

TABLE 4—*Effect of an Abdominal Binder*

Case	Blood Pressure, Recumbent		Blood Pressure, Standing		Symptoms, Erect	
	Without Binder	With Binder	Without Binder	With Binder	Without Binder	With Binder
1			46/40	46/40	Dizziness	Dizziness
2	144/85	144/86	84/56	102/66	Dizziness	0
3	124/85	126/83	56/40	85/40	Dizziness	0

by the calcium chloride method was essentially unchanged but that in those unable to maintain adequate postural adaptation it tended to be slowed. The changes in the circulation time which we found were comparable with the change in cardiac output and did not suggest a marked decrease in the blood flow. The femoral arteriovenous oxygen differences may be considered an index of the blood flow through the legs, i e, as the oxygen difference decreases the blood flow increases. Normally, the arteriovenous difference increases markedly when a change is made from the recumbent to the erect position.<sup>13</sup> The changes

11 (a) Grollman, A. The Effect of Posture on the Output of the Human Heart, *Am J Physiol* **86** 285, 1928. (b) Schellong, F, and Heinemeier, M. Ueber die Kreislaufregulation in aufrechter Körperstellung und ihre Störungen, *Ztschr f d ges exper Med* **89** 49 and 61, 1933. (c) Schneider, E C, and Crampton, C B. The Effect of Posture on the Minute Volume of the Heart, *Am J Physiol* **110** 14, 1934.

12 Bock, A V, Dill, D B, and Edwards, H T. On the Relation of Changes in Blood Velocity and Volume Flow of Blood to Change of Posture, *J Clin Investigation* **8** 535, 1930.

13 Florkin, M, Edwards, H T, and Dill, D B. Oxygen Utilization in the Legs of Normal Men. I. Effect of Posture, *Am J Physiol* **94** 459, 1930.

found in cases 2 and 3 were within the range of normal. Recent work on the effect of posture on the venous pressure<sup>14</sup> indicates that it is essentially unchanged. Formerly it was thought that the venous pressure tends to rise when the erect position is assumed.<sup>15</sup> McIntire and Turner<sup>14</sup> have emphasized the necessity of putting a support behind the subject's shoulders. The present studies were performed without a support, and the results may be considered within normal limits. Lian and Blondel<sup>2k</sup> found the same changes in venous pressure in a subject with postural hypotension as those obtained in normal subjects. It is

TABLE 5—*Circulatory Measurements on Patients with Postural Hypotension*

Case	Position	Average Blood Pressure, Mm of Mercury	Average Heart Rate	Oxygen Consumption, Cc per Min	Cardiac Output,* Liters per Min	Arterio-venous Oxygen Difference in Leg, Vol %	Circulation Time,† Arm to Head, Seconds	Venous Pressure in Arm,‡ Cm of Water	Blood Volume,§ % of Body Weight
1	Horizontal	120/84	86					8	
	Vertical	65/52	92					12	
2	Horizontal	154/80	73	183	{2.60 3.12	7.17	19.5	4	
	Vertical	91/62	75	234	{2.83 2.10	10.36	24	10	
				232	{2.65 2.64				
3	Horizontal	121/82	68	218	{3.70 3.46	1.46	21	9.5	6.55
				221	2.85				
				217	2.70				
				260	{2.84 2.76				
	Vertical	58/44	82	283	2.48	10.86	28	9.5	5.78
				276	2.28				

\* By acetylene method (Grollman, A. *Am J Physiol* **88**:432, 1929)

† By cyanide method (Robb, G. P., and Weiss, S. *Am Heart J* **8**:650, 1933)

‡ By method of Moritz and von Tabora (Moritz, F., and von Tabora, D. *Deutsches Arch f klin Med* **98**:475, 1910)

§ By vital red method (Keith, N. M., Rowntree, L. G., and Geraghty, J. T. A Method for the Determination of Plasma and Blood Volume, *Arch Int Med* **16**:547, 1915)

known<sup>16</sup> that prolonged standing tends to reduce the plasma volume by the escape of fluid into the tissues. In case 3 the change in the blood volume was not significant.

14 McIntire, J. M., and Turner, A. H. Venous Pressure and Posture in Normal Young Women, *J Clin Investigation* **14**:16, 1935

15 Barach, J. H., and Marks, W. L. Effect of Change of Posture—Without Active Muscular Exertion—on the Arterial and Venous Pressures, *Arch Int Med* **11**:485 (May) 1913

16 Thompson, W. O., Thompson, P. K., and Dailey, M. E. The Effect of Posture upon the Composition and Volume of the Blood in Man, *J Clin Investigation* **5**:573, 1928. Waterfield, R. L. The Effects of Posture on the Circulating Blood Volume, *J Physiol* **72**:111, 1931

*Electrocardiogram*—Electrocardiograms taken with the subject in a horizontal and in a vertical position were obtained in cases 1 to 3. They all showed normal results, and, except for minor shifts in the axis and in case 2 a slight decrease in amplitude when the subject was erect, they showed no differences in the two positions. This is in agreement with most of the findings reported in the literature. In the case reported by Sanders,<sup>23</sup> however, there were slight differences in the origin of the T waves and in the elevation of the P waves in the two positions.

TABLE 6—*The Effects of Drugs on Patients with Postural Hypotension in Horizontal and Vertical Positions*

		Blood Pressure, Mm of Mercury				Heart Rate			
		Before		After		Before		After	
Case	Dose, Mg	Horizontal	Vertical	Horizontal	Vertical	Horizontal	Vertical	Horizontal	Vertical
Atropine sulfate									
2	15 i v	174/88	102/69	165/90	100/74	74	78	82	88
	40 i v	128/72	94/56	144/78	75/54	72	80	80	80
3	15 i m and i v	114/79	55/46	142/98	60/48	65	75	82	90
4	0.5 i v	120/66	62/42	140/80	86/60	74	85	80	86
5	0.5 i v	120/82	75/60	132/92	106/80	102	108	113	116
Pilocarpine hydrochloride									
2	7.5 s c	126/70	62/48	136/78	70/48	72	80	76	76
3	7.5 s c	122/82	64/48	145/93	108/78	68	84	80	85
	15.0 s c	114/77	74/46	130/85	104/70	66	80	84	85
Epinephrine hydrochloride									
1	1.3 s c	105/71	*	122/70	70/60	85		96	110
2	1.3 s c	170/84	78/60	180/85	95/65	71	76	80	80
3	1.0 s c	118/80	58/46	148/70	62/38	69	84	96	96
4	1.0 s c	132/62	90/56	147/70	95/48	72	85	86	86
5	1.0 s c	123/79	94/60	126/77	100/65	110	114	112	114
Ergotamine tartrate									
2	1.0 s c	110/60	68/50	182/90	174/86	77	80	70	70
3	0.5 s c	136/90	80/60	150/92	105/76	56	78	56	66

\* Control on another day: blood pressure, 120/84 (horizontal) to 65/55 (vertical), pulse rate 86 (horizontal) to 100 (vertical).

*Pharmacologic Observations*—Atropine (Table 6). In three of the four patients studied atropine administered intravenously in moderate doses failed to increase the heart rate significantly, although its general effects on the pupils and salivation were manifest. In the fourth patient a fairly large dose (1.5 mg intravenously) increased the heart rate less than was expected. In case 2 the drug was administered to the limits of the patient's tolerance (4 mg intravenously within twenty minutes) with little effect on the heart rate. The blood pressure with the patient recumbent was increased in all cases, but in only one of the four was

the fall in pressure when the patient stood lessened, and in no instance were the symptoms alleviated This is in agreement with previous observations <sup>17</sup>

Pilocarpine (Table 6) In cases 2 and 3 pilocarpine hydrochloride in doses of 1/8 and 1/4 grain (8 and 16 mg ), respectively, administered subcutaneously produced sweating, showing that the anhidrosis of these patients was not due to a deficiency of the sweat glands themselves or of their innervation This confirms previous observations <sup>18</sup>

TABLE 7—*The Effect of Ephedrine Sulfate on Patients with Postural Hypotension in Horizontal and Vertical Positions*

Case	Dose, Mg *	Time	Blood Pressure, Mm of Mercury		Heart Rate		Symptoms
			Horizontal	Vertical	Horizontal	Vertical	
1	45	Before After					Dizziness Dizziness
2	22	Before	140/76	70/60	78	80	Temporary dizziness
		After	164/92	96/65	78	78	No dizziness
	45	Before	142/80	90/68	76	80	Dizziness
		After	138/80	94/64	76	82	No dizziness
	45	Before After	176/94 144/80	80/64 73/62	84 84	85 90	Slight dizziness, "all gone" feeling Faintness but no dizziness
3	22	Before	112/75	52/36	72	84	Dizziness
		After	152/92	115/82	74	92	No dizziness
	22	Before	117/77	33/26	62	80	Dizziness, cannot stand
		After	122/81	36/30	78	116	No dizziness, difficulty in seeing and hearing
	22	Before	136/88	65/50	75	90	No dizziness
		After	152/90	99/70	70	96	No dizziness
	45	Before After	124/76 166/96	84/58 123/85	98 70	103 104	Buzzing in ears, eyes blurred No symptoms
4	22	Before	126/66	64/50	76	84	Dizziness
		After	126/68	106/70	70	80	No dizziness
5	22	Before	120/76	78/58	101	110	Transient dizziness
		After	122/78	91/70	104	108	No dizziness

\* Administered orally

Epinephrine (Table 6) The fall in blood pressure was in no case prevented by epinephrine, and the symptoms persisted, except in case 2, in which dizziness was relieved The only atypical effect of this drug noted was that the heart rate of these patients tended to increase less than one would expect from the dose given

Ephedrine (Table 7) This drug abolished the dizziness of four of the five patients to whom it was administered It is of interest that the relief of symptoms occurred irrespective of whether or not ephedrine lessened the fall in blood pressure when the patient stood

17 Bradbury and Eggleston <sup>1</sup> Ghrist and Brown <sup>2a</sup> Sanders <sup>2g</sup> Weis <sup>2o</sup>

18 Bradbury and Eggleston <sup>1</sup> Barker <sup>21</sup>

Ergotamine (Table 6) In cases 2 and 3 ergotamine greatly lessened the drop in blood pressure. One patient (case 2), however, stated that the dizziness or "all gone" feeling was still present when she stood, but the interpretation of the effectiveness of the drug was hindered by the marked substernal distress which occurred and which was of sufficient severity to make inadvisable a repetition of the procedure.

*Postural Reflex in Neurologic Disease*—Four of the patients showed extensive lesions of the central nervous system. In one there was

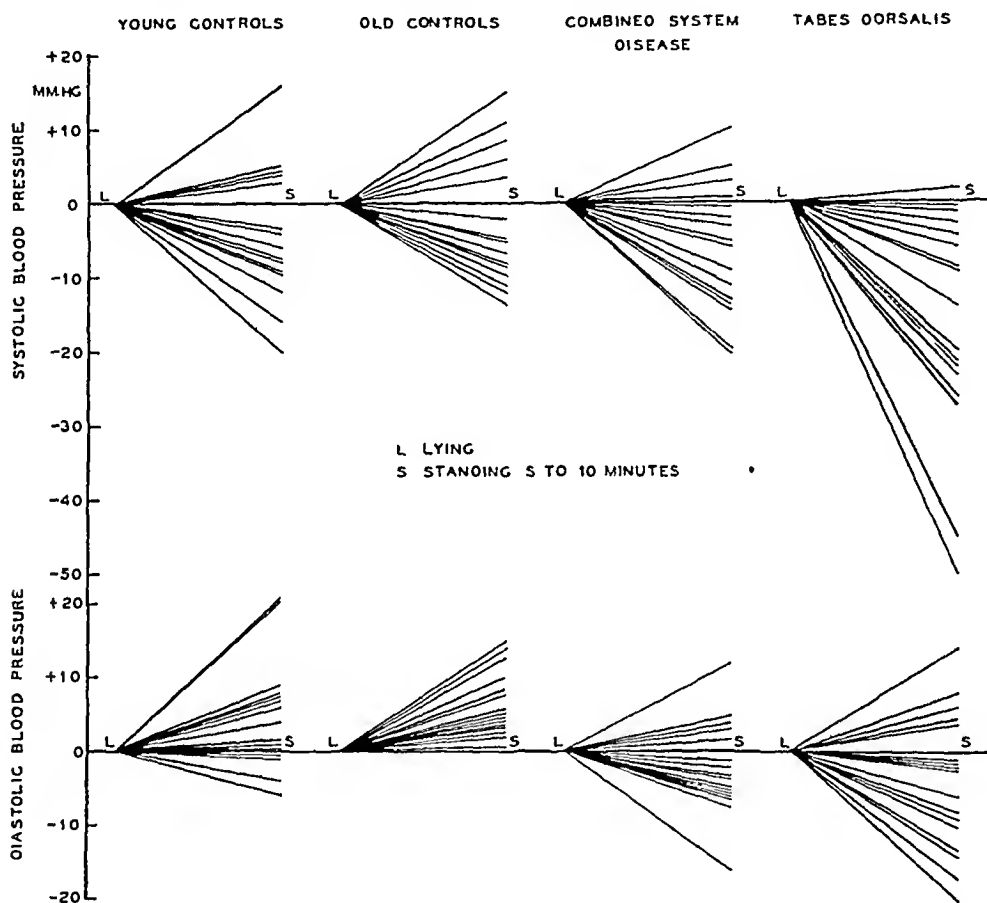


Chart showing the effect of standing on the systolic and diastolic blood pressures of control subjects and of patients with combined system disease or with tabes dorsalis

definite, although not marked, evidence of disease of the central nervous system, while only one did not show any evidence of organic neurologic disease. In addition to these cases the postural changes in blood pressure in a group of patients with neurologic disease were studied. Repeated measurements were made with the patient recumbent and with the patient standing quietly for ten minutes. The blood pressure readings given in the accompanying chart represent the averages obtained in the period from five to ten minutes after the subject had stood up.



Two groups of control subjects were chosen a group of healthy young adults ranging in age from 18 to 35 years and a group of older persons from 41 to 89 years old, all of whom were ambulatory hospital patients suffering from minor disorders, with no evidence of neurologic disease and no disturbance of the cardiovascular system other than the amount of arteriosclerosis consistent with their respective ages. The patients with *tabes dorsalis* all had Argyll Robertson pupils, those with combined system disease were ambulatory and no patient in either group had hypertension. Cases 4 and 5 are included among the charted cases of *tabes dorsalis*.

Our blood pressure findings in the two control series are in agreement with the results of other investigations on normal persons when allowance is made for the fact that most of the studies in the past have been made with the patient's arm at his side when he was erect. Our determination of the blood pressure with the patient standing and the arm supported at the level of the heart makes the average blood pressure, both systolic and diastolic, in this position about 3 or 4 mm. of mercury lower than it would be with the arm at the side.

None of the subjects with combined system disease showed definite postural hypotension. Although as a group they tended to show a somewhat greater drop than normal in the systolic blood pressure and a slight fall in the diastolic pressure, the deviations from normal were not sufficiently great to permit the conclusion that there was any disturbance of the sympathetic postural reflex.

The abnormal responses observed in the group of subjects with *tabes dorsalis* were more striking. In addition to the two patients with definite postural hypotension, there were three in whom the systolic pressure fell 20 mm. or more when they stood and the diastolic dropped 5 mm. or more. In five other patients either the systolic or the diastolic pressure fell abnormally. Thus in ten of seventeen patients with *tabes dorsalis* there was an abnormal postural response in the blood pressure.

In addition to these groups a miscellaneous group of subjects with disease of the central nervous system was studied. In none of them was the response of the blood pressure abnormal. These patients suffered from the following diseases: two had moderately advanced multiple sclerosis without evident cerebral involvement, one had marked syringomyelia including involvement of the cervical portion of the sympathetic chain on the left, one had amyotrophic lateral sclerosis, three had had transverse myelitis but the condition had improved so that they were able to walk and one patient with a Brown-Séquard syndrome from a cervical lesion had improved so that he was ambulatory.

## COMMENT

*The Normal Control of Blood Pressure* —The arterial blood pressure is controlled by the interrelation of three important factors the output of the heart, the volume of the circulating blood and the peripheral vascular resistance. Perhaps the most important of these factors is the peripheral vascular resistance, the chief site of which is in the arterioles and to a lesser extent in the capillaries and possibly the venules. The degree of tone of the blood vessels which determines the resistance is partly an inherent property of the muscle itself, partly dependent on the nervous influences coming to it through the vasomotor nerves and partly influenced by circulating hormones.

The nervous control of the blood pressure is affected indirectly through the nervous influence on the heart rate and directly through the vasomotor nerves to the blood vessels by vasoconstriction and to some extent by active vasodilatation. It is possible that sympathetic centers exist in the spinal cord which have to do with the vasomotor tone, since it is known that the vascular tone below the level of an injury is regained in a patient who has suffered traumatic transection of the spinal cord, as well as in an animal with an experimentally severed spinal cord. The chief centers for the vasomotor control, however, lie in the brain. It has been shown<sup>19</sup> that vasoconstrictor centers exist in the floor of the fourth ventricle. Sympathetic and possibly parasympathetic centers also are present in the hypothalamus,<sup>20</sup> which are in part concerned with the vasomotor tone. Finally, a certain amount of control over the vasomotor reactions is exercised by the cerebral cortex, from centers probably confined to the premotor area.<sup>21</sup>

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19 Ranson, S W, and Billingsley, P R. Vasomotor Reactions from Stimulation of Floor of Fourth Ventricle, *Am J Physiol* **41** 85, 1916

20 Karplus, J P, and Kreidl, A. Gehirn und Sympathicus. II. Ein Sympathicuszentrum im Zwischenhirn, *Arch f d ges Physiol* **135** 401, 1910, Gehirn und Sympathicus. IV Mitteilung, *ibid* **171** 192, 1918, Gehirn und Sympathicus. VII Ueber Beziehungen der Hypothalamuszentren zu Blutdruck und innerer Sekretion, *ibid* **215** 667, 1927. Beattie, J, Brow, G R, and Long, C N H. Physiological and Anatomical Evidence for the Existence of Nerve Tracts Connecting the Hypothalamus with Spinal Sympathetic Centres, *Proc Roy Soc, London, s B* **106** 253, 1930. Ranson, S W, Kabat, H, and Magoun, H W. Autonomic Responses to Electrical Stimulation of Hypothalamus, Preoptic Region and Septum, *Arch Neurol & Psychiat* **33** 467 (March) 1935

21 Eulenberg, A, and Landois, L. Ueber die thermischen Wirkungen experimenteller Eingriffe am Nervensystem und ihre Beziehung zu den Gefassnerven, *Virchows Arch f path Anat* **68** 245, 1876. Danielopolu, D, Radovici, A, and Aslan, A. Einfluss der Hirnrinde auf die Vasomotoren, *Ztschr f d ges Neurol u Psychiat* **132** 671, 1931. Pinkston, J O, Bard, P, and Rioch, D McK. The Responses to Changes in Environmental Temperature After Removal of Portions of the Forebrain, *Am J Physiol* **109** 515, 1934. Kennard, M A. Vasomotor Disturbances Resulting from Cortical Lesions, *Arch Neurol & Psychiat* **33** 537 (March) 1935

*The Normal Postural Adaptation of the Blood Pressure*—When a human being undergoes marked postural changes, as in rising from a recumbent to an erect position, alterations must occur in the cardiovascular system in order to compensate for the altered hydrostatic conditions<sup>22</sup> The compensation is usually prompt and adequate, so that only minor changes occur in the blood pressure and heart rate The systolic blood pressure remains essentially unchanged, it may rise or fall slightly but rarely more than 10 mm of mercury The diastolic blood pressure usually increases slightly, and the pulse pressure in consequence is somewhat decreased The heart rate increases from 10 to 20 beats per minute Although perhaps it has not been proved, the evidence points to the fact that this is accomplished by means of sympathetic stimulation of the heart and blood vessels The site of the vasomotor center involved is not definitely known

*Physiologic Variations in Postural Adaptation*—Under certain physiologic conditions the postural adaptation of the blood pressure may be inadequate and may even result in symptoms such as dizziness or fainting due to cerebral anemia When this adaptation is insufficient, the inadequacy may occur immediately on assumption of the upright position, with subsequent full compensation, or, more commonly, the initial compensation is excellent but as standing is maintained the adaptation gradually becomes inadequate<sup>23</sup> In the latter case, as the erect position is maintained the systolic pressure falls steadily, although not markedly, the diastolic pressure usually is maintained or may even progressively increase and the heart rate increases continuously Dizziness or fainting may occur sooner or later and often comes on with great abruptness In some instances the postural vasomotor reflex may be delayed, as when there is a temporary initial fall in the blood pressure, or it may occur with insufficient intensity In most cases, however, the chief cause is impairment of the intrinsic vascular tone or poor tone in the skeletal musculature, especially of the abdomen and legs The postural reflex operates not only normally but often excessively, as

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22 (a) Schellong and Heinemeier<sup>11b</sup> (b) Ellis, L B, and Haynes, F W Personal observations (c) Ellis, M M Pulse Rate and Blood Pressure Responses of Men to Passive Postural Changes, *Am J M Sc* **161** 568, 1921 (d) Schneider, E C, and Truesdall, D A Statistical Study of the Pulse Rate and the Arterial Blood Pressures in Recumbency, Standing, and After a Standard Exercise, *Am J Physiol* **61** 429, 1922 (e) Turner, A H The Adjustment of Heart Rate and Arterial Pressure in Healthy Young Women During Prolonged Standing, *ibid* **81** 197, 1927 (f) Ghrist, D G Variations in Pulse and Blood Pressure with Interrupted Change of Posture, *Ann Int Med* **4** 945, 1931 (g) Turner, A H, Newton, M I, and Haynes, F W The Circulatory Reaction to Gravity in Healthy Young Women Evidence Regarding Its Precision and Its Instability, *Am J Physiol* **94** 507, 1930

23 Schellong and Heinemeier<sup>11b</sup> Ghrist<sup>22f</sup> Turner, Newton and Haynes<sup>22g</sup>

shown by the marked tachycardia and maintenance of or even increase in the diastolic pressure. Nevertheless, blood continues to pool in the dependent venous areas, gathering there either because of a deficient venous tone or because of failure of the skeletal muscles to assist properly in the venous return. The heart receives and pumps progressively less blood, until finally cerebral anemia results.

This deficient postural adaptation is seen frequently in persons convalescent from a severe infection and in persons debilitated from any cause whatever. Patients with marked vasomotor instability are likely to exhibit it. Lewis<sup>24</sup> has commented on its occurrence in cases of effort syndrome. Mild degrees of insufficient adaptation are especially likely to result in symptoms when, in addition, other factors tending to promote cerebral anemia exist, e g, cerebral arteriosclerosis or an initial low blood pressure.

*Postural Hypotension*—Postural hypotension differs from the common type of inadequate postural adaptation. It is characterized by an immediate, marked and persistent fall in both the systolic and the diastolic pressure and frequently by a failure of the usual increase in the heart rate. The physiologic studies of the hemodynamics of the circulation made in cases 2 and 3 indicate that the total blood flow through the body is well maintained.

The only positive finding, therefore, in the physiologic study of the circulation of these patients was the great decrease in the arterial blood pressure. Why, then, does the pressure fall, and why do cerebral symptoms ensue? These subjects evidently fail to have reflex vasoconstriction when in a standing position, which would compensate for the increased hydrostatic pressure. This hydrostatic increment, therefore, tends to cause blood vessels lying below the level of the heart to dilate and to accommodate more blood. As a result there is a shift in the distribution of blood in the vascular bed, and although the heart pumps out an adequate amount, the blood circulates mainly through the dependent areas. The regions above the level of the heart, notably the brain, receive an inadequate circulation, and symptoms ensue. The extent of blood flow through the regions below the level of the heart depends on the result of two opposing factors. On the one hand, the dilatation of the arterioles tends to increase the blood flow, whereas, on the other hand, the dilatation of the capillaries and veins tends to cause temporary stagnation of the blood and a slowed blood flow. Although the possibility cannot be definitely excluded that a paradoxical vasomotor reaction may take place when the patient stands, i e, an active dilatation, it appears unnecessary to predicate such a hypothesis. It is of interest

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24 Lewis, T. *The Soldier's Heart and the Effort Syndrome*, New York, Paul B. Hoeber, Inc., 1919, p. 19.

that the level of the blood pressure at which symptoms first occurred and fainting took place varied greatly in our patients and in those reported in the literature, not only between subjects but in the same person at different times. This variation must be due to alterations in the state of the cerebral blood vessels, that is, to varying degrees of arteriosclerosis, and in the same subject to changes in the cerebral vascular tonus.

The deficiency in the compensatory vasoconstriction involves the vascular areas both of the splanchnic region and of the legs, because the drop in blood pressure is partially abolished by eliminating the circulation through the legs by occluding pressure cuffs.

#### ETIOLOGY

The cause for this disturbance in compensatory postural vasoconstriction lies undoubtedly in a failure of the normal vasomotor reflex to operate. That it is an abnormality in the sympathetic nervous system is suggested also by the frequent occurrence of anhidrosis in these patients. It has been shown that the disturbance is generalized, and therefore either the site of the lesion must be in a sympathetic center or an afferent pathway controlling the entire reflex response or it must be a widespread disturbance of the efferent pathways or nerve endings.

As will be discussed later, it is probable that the etiology of postural hypotension is multiple and that under certain conditions the reflex arc may be interrupted at different levels. An interesting observation in this connection was that of Brown, Craig and Adson,<sup>25</sup> who noted that postural hypotension develops in patients with hypertension when all the sympathetic fibers have been removed from vessels below the diaphragm by resection of the anterior roots from the sixth thoracic to the second lumbar vertebra. Evidence can be presented, however, that in many of the clinical cases the disturbances lie within the central nervous system, probably within the brain. Moreover, postural hypotension of greater or less severity is not an infrequent accompaniment of disease of the central nervous system. It is possible that when the anatomic pathways of this reflex have been traced with greater exactitude, the measurement of blood pressure in different bodily positions may furnish evidence as to the presence or location of a lesion of the central nervous system.

A diminution or absence of the normal acceleration of the heart rate caused by standing is frequently but not invariably seen in association with postural hypotension, and its occurrence tends to aggravate the fall

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<sup>25</sup> Brown, G. E., Craig, W. McK., and Adson, A. W. The Treatment of Severe Essential Hypertension. Effects of Surgical Procedures Applied to the Sympathetic Nervous System, *Minnesota Med* **18** 134, 1935.

in blood pressure. It, too, is undoubtedly due to a sympathetic disturbance which could theoretically be located in the reflex arc involved.

With the exception of case 5, the abnormal responses which have been elicited in patients with orthostatic hypotension can all be explained on the basis of a disturbance of the sympathetic system, without assuming that the parasympathetic system is involved, as suggested by Ghrist and Brown. Failure of the heart to accelerate when the subject stands or after atropinization can be adequately explained by an absence of sympathetic stimulation. In case 5 the persistent tachycardia may have been due to paralysis of the vagus nerve.

1 *The Postural Reflex in Disease of the Central Nervous System* — In their original description of postural hypotension Biadbuay and Eggleston commented on the occurrence of indefinite changes in the central nervous system. Such vague changes were observed also by Ghrist and Brown in one of their cases.

Strisower<sup>20</sup> was the first to point out the association of postural hypotension with tabes dorsalis. He said that he considered the disorder to be due to a disturbance of the vasomotor regulation, probably due to involvement of the centers in the spinal cord which regulate the blood pressure. In addition, he said that he believed that there must also be a depression of the vagus reflex to explain the failure of the heart to accelerate.

Allen and Magee<sup>21</sup> mentioned that the hemianopia and aphasia which occurred in the case cited by them could not be explained by the postural hypotension alone, and they assumed the presence of patchy sclerosis of the cerebral vessels as a cause of these phenomena. The two patients reported on by Gainshorn and Horton<sup>22</sup> exhibited extensive involvement of the central nervous system, including evidence of disturbance of the sympathetic innervation of the brain. The patient cited by Croll, Duthrie and MacWilliam<sup>23</sup> showed a pseudo-Argyll Robertson pupil on one side and absence of the knee jerks, although examination of the spinal fluid revealed no abnormality.

Four of our patients showed marked and one showed definite though slight evidence of disease of the central nervous system. We have shown also that a disturbance of the postural blood pressure reflex is frequently observed in patients with tabes dorsalis, since it occurred in ten of the seventeen patients studied. On the other hand, it is evident from a consideration of the patients with combined system disease and with miscellaneous neurologic lesions that extensive disease of the central nervous system, especially of the spinal cord, can exist without a disturbance of the postural blood pressure reflex.

When a disturbance of this reflex does occur, where is the site of the lesion? The presence of Argyll Robertson pupils in all the cases of tabes was evidence of a disease affecting the brain. The third

patient, who was suffering from syringomyelia, showed definite evidence of involvement of the brain as well as of the cervical region of the spinal cord

Further and conclusive evidence that the postural blood pressure reflex passes through centers in the brain and is not a spinal reflex is presented by case 6, the patient in whom traumatic section in the upper portion of the dorsal region of the spinal cord had occurred. In this patient there was reproduced as nearly as possible in a human being the condition of the "spinal animal," with complete severance of the control of the brain from the spinal cord. The fact that marked postural hypotension occurred in this patient indicates that the reflex arc was interrupted, this undoubtedly having taken place in the pathways leading from the brain.

The exact locus within the brain of the site of the center controlling this reflex cannot be stated with certainty, but it appears most reasonable that it is located in the hypothalamic area. This view is supported not only by the generally held concept that this region is concerned with somewhat more integrative functions than the hindbrain, but also by the fact that in the patients with tabes suffering from a disturbed postural reflex there exists a syphilitic lesion producing the pupillary changes in a region close to the sympathetic center in the hypothalamus<sup>26</sup> which might involve either the center directly or, more probably, the sympathetic fibers coming from it.

The second patient exhibited certain signs consistent with an early stage of combined system disease of the spinal cord but no objective evidence of involvement of the sympathetic centers in the brain. Although it is conceivable that involvement of the efferent sympathetic pathways in the spinal cord occurred which abolished the normal postural reflex, there is no corroborative evidence for this theory. It would be particularly hazardous to stress this theory in view of the fact that the fifteen patients suffering from combined system disease of greater severity than that in case 2 in no instance exhibited a definitely disturbed postural reflex.

*2 The Rôle of the Carotid Sinus*—It has been suggested by Laubry and Doumer,<sup>21</sup> Hering,<sup>27</sup> Heymans,<sup>28</sup> Ask-Upmark<sup>29</sup> and others that

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26 Merritt, H. H., and Moore, M. The Argyll Robertson Pupil. An Anatomic-Physiologic Explanation of the Phenomenon, with a Survey of Its Occurrence in Neurosyphilis, *Arch Neurol & Psychiat* **30** 357 (Aug.) 1933.

27 Hering, H. E. Ueber die Blutdruckregulierung bei Aenderung der Körperstellung vermittle der Blutdruckzugler und das Zustandekommen der Ohnmacht beim plotzlichen Uebergang vom Liegen zum Stehen, *Munchen med Wchnschr* **74** 1611, 1927.

28 Heymans, C., Bouckaert, J. J., and Regniers, P. Le sinus carotidien et la zone homologue cardio-aortique, Paris, Gaston Doin & Cie, 1933, p. 286.

29 Ask-Upmark, E. The Carotid Sinus and the Cerebral Circulation, Lund, Berlingska Boktryckeriet, 1935, p. 266.

failure of the postural adaptation may be due to a disturbance of the regulating function of the carotid sinus and aortic depressor nerve. It has been shown<sup>27</sup> that in experimental animals in which denervation of these areas has been carried out postural hypotension occurs. In spite of the suggestiveness of this finding, it is not justifiable to apply the conclusions unequivocally to human beings. Since man, in contrast to the lower animals, is constantly subjecting himself to marked changes in bodily position, he may have acquired a more intricate or widespread postural reflex. The possibility that other vascular regions than the carotid sinus or the aortic arch may be concerned in initiating this reflex in human beings cannot be excluded<sup>30</sup>. Although there is no direct evidence that hypo-excitability of the carotid sinus is at times responsible for postural hypotension in human beings, the possibility cannot be excluded. In our cases the evidence that was available was against the hypothesis that a lesion of the carotid sinus is etiologically responsible.

3 *Disturbances of the Endocrine Glands*—Several instances of postural hypotension associated with disease of the endocrine glands have been reported. Duggan and Barr<sup>28</sup> studied a patient with Addison's disease who showed a marked drop in blood pressure when he stood, with associated vomiting and extreme dizziness. Ghrist<sup>22f</sup> has shown that a certain proportion of the patients with Addison's disease react to postural change with a marked fall in the blood pressure and an exaggerated rise in the pulse rate. In case 1 of the present series, although a diagnosis of Addison's disease could not be definitely made, there was considerable clinical and pathologic evidence favoring the diagnosis of a destructive lesion of the adrenal cortex. In view of the absence of other demonstrable etiologic factors, it is possible that such a lesion may have been responsible for the postural hypotension in this case. The reaction may in part be due to general hypofunction of the sympathetic nervous system and in part to the generalized muscular hypotonicity and weakness which are noted in this condition and which in themselves would hinder the adequate return of venous blood with the subject in the erect position.

A relationship between postural hypotension and hypofunction of the pituitary gland has been claimed by Schellong<sup>2d</sup>. He has found that this syndrome occurs in patients with clinical features suggesting Simmonds' disease and that it may be relieved by injections of a preparation of the anterior lobe of the pituitary gland. The evidence presented by Schellong of unequivocal diseases of the pituitary gland in his cases and of specific relief following the administration of an extract of the anterior lobe of the pituitary gland is insufficient to warrant a definite

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30 MacWilliam, J. A. Postural Effects on Heart-Rate and Blood-Pressure, *Quart J Exper Physiol* **23** 1, 1933



ascription of an etiologic rôle to the pituitary gland. However, it is possible that certain disturbances of the glands of internal secretion may so affect the functioning of the vasomotor system that postural hypotension occurs.

4 *Toxic Agents or Trauma*—Whether toxic agents or trauma ever produce postural hypotension is uncertain. One of the cases of this syndrome which have been reported<sup>4</sup> apparently followed a blow in the abdomen, and in another<sup>28</sup> the symptoms were initiated by the sensation of something breaking loose in the abdomen. This raises the question of whether the structure of the splanchnic nerve may not have been damaged. Tipodi<sup>3</sup> has ascribed the cause in one of his cases to over-indulgence in tobacco smoking, but the evidence in this instance that tobacco was the etiologic agent is unconvincing.

In the light of the accumulated evidence, therefore, it may be considered that postural hypotension is a syndrome of multiple etiology. Frequently it is caused by demonstrable disease of the central nervous system, which either involves the sympathetic centers or acts on the sympathetic pathways. Disease of the endocrine glands, especially the adrenal cortex, may in certain instances be associated with this condition. In some cases, often when the symptoms are transitory, the syndrome may occur in vasomotor neurosis or during severe nervous exhaustion.<sup>21</sup> Whether trauma or external toxic agents cause it is as yet uncertain. Finally, there remains a group of patients showing postural hypotension in whom no specific etiologic cause can be found. For the present, the term idiopathic must be employed for the condition in this group. Whether in any of these cases the condition is due to hypo-excitability of the carotid sinus cannot be stated, but there is no direct evidence in favor of this possibility.

#### TREATMENT

The treatment of postural hypotension resolves itself into three aspects: treatment of the underlying condition, mechanical measures and drug therapy.

If an etiologic cause can be demonstrated, it should be vigorously treated if possible. Mechanical measures, such as tight bandaging of the legs or abdomen or both, sometimes offer considerable relief. Physical therapy may justifiably be given to a patient with general debility or nervous exhaustion, but otherwise it has been found to be of little or no value.

The most valuable pharmacologic agent which has been employed is ephedrine. Its use was originally suggested by Ghrist and Brown. In about half the cases in which it was tried the drug has given symptomatic relief. The usual dose employed is from 25 to 50 mg. by mouth as frequently as necessary. It has been assumed that the beneficial effect of ephedrine lies in its action in lessening the fall in the blood

pressure when the patient is in the erect position and in maintaining it above a critical level. While a certain amount of the improvement may be due to this peripheral effect, it is probable that the central action of ephedrine on the brain cells or cerebral circulation also plays an important rôle, and in some instances at least it is entirely responsible for the resulting benefit. This is demonstrated in our cases, as well as in the case reported by Baikei and Coleman, in which dizziness was abolished after the administration of 25 mg of ephedrine sulfate, regardless of whether the blood pressure fell to the same level when the patient stood as it did before the drug was given. It is known that ephedrine exerts a central action, the nature of which is not understood, and that it is used with benefit in certain cases of narcolepsy.

Ergotamine tartrate, when administered parenterally, lessens the postural hypotension and may relieve the dizziness to some extent. The use of this drug for this purpose was first suggested by Barker.<sup>21</sup> This effect is probably gained through the direct constricting action of the drug on the walls of the vessels. The likelihood of unpleasant side-effects, its relatively transitory action and the necessity of administering the drug by injection limits its usefulness.

A preparation of the anterior lobe of the pituitary gland, has been employed with apparent benefit by Schellong<sup>22</sup> and Rudsit,<sup>4</sup> but the results were not sufficiently convincing to be accepted without further confirmation.

#### SUMMARY AND CONCLUSIONS

Six cases of postural hypotension are reported. In four there was definite evidence of neurologic disease (tabes dorsalis, syringomyelia and hematomyelia), and in an additional case there was some evidence of involvement of the central nervous system.

The vascular responses were tested, and in two patients measurements of the circulatory dynamics were made. The total blood flow was found to be well maintained when the patient was in the erect position.

The effects of atropine, pilocarpine, epinephrine, ergotamine and ephedrine were studied. Ephedrine was the most effective in relieving the symptoms.

The effect of postural change on the blood pressure of patients with tabes dorsalis, combined system disease and miscellaneous neurologic lesions was studied. Ten of seventeen successive patients with tabes had an abnormal postural response of the blood pressure.

✓ The etiology and mechanism of postural hypotension are discussed. Postural hypotension results from a failure of the normal sympathetic vasomotor reflex to produce vasoconstriction when the subject assumes an erect position. It has been shown that the center controlling this reflex lies in the brain and not in the spinal cord. ✓ Since the disturbance

is widespread, the site of the lesion is either in a sympathetic center or in an afferent pathway controlling the entire response, or it is generalized throughout the efferent pathways or nerve endings. It is probable that multiple etiologic causes exist, but many instances of postural hypotension are associated with disease of the central nervous system.

NOTE—Since the submission of this article for publication several additional papers on postural hypotension have been published or have come to our attention. Hughes and Yusaf<sup>31</sup> have reported a case, which, however, is more suggestive of poor adaptation than of true failure of the postural reflex. Alvarez and Roth<sup>32</sup> and Bickel and Demole<sup>33</sup> have each reported an additional case, and the latter authors have stressed, as have we, the importance of disease of the central sympathetic centers and pathways in the etiology of the condition. Bickel and Demole have also cited certain references on the subject, the originals of which are not available to us. Another reference which we have been unable to consult is that of Colombatti and Springer<sup>34</sup>.

Dr Tracy J. Putnam, of the Neurologic Service, and Dr Donald Munro, of the Neurosurgical Service, gave permission for the publication of the reports of cases 1, 3, 4 and 6. Drs R. B. Capps and E. B. Ferris Jr. made certain of the observations on the vascular responses.

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31 Hughes, T. A., and Yusaf, M. *Lancet* **1** 1101, 1935.

32 Alvarez, W. C., and Roth, G. *Proc. Staff Meet., Mayo Clin.* **10** 483, 1935.

33 Bickel, G., and Demole, M. *Rev. méd. de la Suisse Rom.* **56** 1, 1936.

34 Colombatti, M., and Springer, G. *Gior. med. d. Alto Adige* **7** 364, 1935.

# TREATMENT OF TYPHOID WITH AN ANTI-TOXIC ANTITYPHOID SERUM

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DETROIT

The preparation of any standardized antitoxic serum of a reliable concentration depends on the possibility of measuring the antitoxic content of the serum in terms of its power to prevent specifically a biologic reaction to a definite amount of toxin. The lack of such a specific biologic phenomenon for the detection and measurement of the toxins derived, for instance from *Bacillus typhosus*, *Meningococcus*, *Bacillus coli* and Pfeiffer's bacillus, has served to delay the preparation of therapeutic serums of uniform potency. With serums such as the antimeningococcic serum, which are presumed to owe their therapeutic value to the presence of bactericidal properties, the possibility exists that the presence of undetermined amounts of antitoxin may explain the generally recognized variability in therapeutic efficacy<sup>1</sup>

The discovery by one of us (G S<sup>2</sup>) of the phenomenon of local cutaneous reactivity to bacterial filtrates has offered a new biologic reaction by means of which a soluble antigenic toxin can be recognized in bacteria hitherto assumed to produce only endotoxins of poor antigenicity. Conversely, it has been shown that the antitoxic content of a therapeutic serum can be precisely measured by its ability to neutralize or prevent specifically the biologic effect of the toxin.

In its application to the culture filtrates of *B typhosus* this phenomenon has made it possible also to demonstrate the existence of *B typhosus* toxic substances identical or closely related to true exotoxins<sup>3</sup>. These soluble bacterial substances were obtained under con-

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1 Schwartzman, G. Therapeutic Antimeningococcus Serum, *J A M A* **93** 1965 (Dec 21) 1929

2 Schwartzman, G. *J Exper Med* **48** 247, 1928

3 Schwartzman, G. *J Exper Med* **49** 593, 1929, **50** 513, 1929, **54** 1, 1931, *Klin Wchnschr* **9** 41, 1925 and 1974, 1930

ditions which allow little cell autolysis (in young "agar washings" cultures) By the injection of the filtrates into large animals immune antitoxic serums were developed which neutralize the toxic substances specifically and in multiple proportions <sup>3</sup>

#### PREVIOUS OBSERVATIONS

Attempts to develop a specific serum therapy for typhoid have been made by numerous investigators The difficulties encountered in the past were mainly due to the lack of a specific biologic reaction for measuring the potency of the therapeutic serums employed (horse, goat and sheep) Estimation of their therapeutic potency was usually based on the agglutination titer of the serum In some instances (Berner Institute serum [Tavel] used by Spirig <sup>4</sup> and Du Mesnil <sup>5</sup>) bacteriolysis and antiendotoxic tests (Chantemesse, <sup>6</sup> Kraus and Stenitzer <sup>7</sup> and Besredka <sup>8</sup>) were employed as well as protection tests against live *B. typhosus* cultures in guinea-pigs (Klemperer and Levy, <sup>9</sup> Rodet, <sup>10</sup> Grasset and Gory <sup>11</sup> and Ludke <sup>12</sup>) Favorable therapeutic results were reported with some of the serums (Chantemesse and Widal, <sup>13</sup> Kraus and Stenitzer, <sup>14</sup> Rodet, <sup>15</sup> Berner Institute serum, <sup>16</sup> Burroughs and Wellcome serum, <sup>17</sup> Grasset and Gory serum <sup>11</sup> and the Besredka serum used by Andriescu and Ciuca <sup>18</sup>), especially if they were administered in the early stages of the disease, usually during the first two weeks The reports of subsequent investigators seem to have discredited some of these claims (Bertoye and Etienne Martin <sup>19</sup> with Rodet's serum)

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- 4 Spirig, W    *Cor-Bis f. Schweiz Aerzte* **28** 385, 1898
  - 5 Du Mesnil    *Munchen med Wchnschr* **49** 1238, 1902
  - 6 Chantemesse, A    *Gaz d. hop* **71** 397, 1898
  - 7 Kraus, R., and von Stenitzer, R    *Wien klin Wchnschr* **20** 344, 1907
  - 8 Besredka, A    *Ann Inst Pasteur* **20** 149, 1906
  - 9 Klemperer, F., and Levy, E    *Berl klin Wchnschr* **32** 601, 1895
  - 10 Rodet, A    *J State Med* **22** 79, 1914
  - 11 Grasset, E., and Gory, M    *Compt rend Soc de biol* **98** 435, 1928    Grasset, E    *J M A South Africa* **4** 380, 1930
  - 12 Ludke, H    *Munchen med Wchnschr* **59** 907, 1912
  - 13 Chantemesse, A    *Bull et mem Soc med d. hop de Paris* **36** 11, 1913  
Brunon    *Bull Acad de med, Paris* **45** 275, 1906    Josias, A    *Med mod* **13** 181, 1902
  - 14 Kraus, R., and von Stenitzer, R    *Deutsche med Wchnschr* **37** 577, 1911.  
Forsmann    *ibid* **37** 1936, 1911
  - 15 Rodet <sup>10</sup> Etienne, G., and Gerbaut    *Rev med de l'est* **61** 445, 1933  
Louyot    *ibid* **61** 449, 1933    Remond, A., and Minvielle    *Bull Acad de med, Paris* **73** 321, 1915
  - 16 Spirig <sup>4</sup> Du Mesnil <sup>5</sup>
  - 17 Pope, F M    *Brit M J* **1** 259, 1897    Cooper, P R    *ibid* **1** 518, 1897.  
Baskett, B    *ibid* **1** 423, 1903    Cowen, T R J    *Lancet* **2** 778, 1899
  - 18 Andriescu, C., and Ciuca, M    *Ann Inst Pasteur* **27** 170, 1913
  - 19 Bertoye, P., and Martin, P E    *Lyon med* **143** 723, 1929

The therapeutic value of these antityphoid immune serums has been discredited on other grounds also. The antibodies which were demonstrable in the serums (bacteriolysins, agglutination and complement-fixing antibodies) apparently have no bearing on the processes of recovery from an acute infectious disease. The so-called antiendotoxic serums fail to neutralize these endotoxins specifically and in multiple proportions. The effect of endotoxins on test animals were shown by Pfeiffer and Bessau,<sup>20</sup> Zinsser<sup>21</sup> and more recently by Murray<sup>22</sup> to be irregular in their effect.

The interesting results obtained with the serum of Giasset and Gory<sup>11</sup> depended on the protection of guinea-pigs against subcutaneous infections with live *B. typhosus*. Unfortunately, no accurate determination of the potency of the serum is possible under the experimental conditions described by these authors.

#### TECHNIC

The following methods were employed in the preparation of the antityphoid antitoxic serum employed by us in the treatment of typhoid and in the determination of its potency before therapeutic trial.

Horses were immunized for several months by weekly subcutaneous and intravenous injections. Some of the serums recently employed were obtained from horses which had received two or three weekly injections. For the subcutaneous injections bacteria-free filtrates, "agar washings" culture filtrates and in some instances tryptic-digest broth culture filtrates of *B. typhosus* were used. The initial dose varied from 1 to 5 cc, and the amount was gradually increased to 20 cc. For the intravenous injections heat-killed vaccines of several strains of *B. typhosus* were used. The initial dose was from 3 to 5 cc of vaccine containing approximately 1,000,000,000 micro-organisms per cubic centimeter. On subsequent injections the dose was gradually increased to 10 cc. Higher concentrations of the vaccine were then made, containing 5,000,000,000 micro-organisms per cubic centimeter, and the dose was gradually increased until 10 cc was finally used. It is possible to continue the immunization of horses with *B. typhosus* culture filtrates and vaccines in this manner for a considerable length of time. It should be remembered, however, that the materials are toxic. Sometimes, a small amount of filtrate kills a horse. Rises in temperature, cutaneous abscesses and systemic shock are frequently observed. In case of shock a horse can often be saved by epinephrine given immediately or within a few hours after the injection of the immunizing material and later by large bleedings. The abscesses are easily relieved by incision and the evacuation of pus.

The ability of a horse to produce antibodies is subject to considerable individual variation. Moreover, antibodies capable of neutralization of the phenomenon under discussion may unexpectedly drop in titer. For this reason, it seems impor-

20 Pfeiffer, R., and Bessau, G. *Zentralbl. f. Bakt. (Abt. 1)* **56** 344, 1910.

21 Zinsser, H., Parker, J. T., and Kuttner, A. *Proc. Soc. Exper. Biol. & Med.* **18** 49, 1921.

22 Murray, E. G. D. *The Meningococcus*, Medical Research Council, Special Report Series, no. 124, London, His Majesty's Stationery Office, 1929.

tant that the large bleeding be made as quickly as possible after the trial bleeding. This is carried out as follows. The necessary groups of rabbits are prepared by intradermal injections of the *B typhosus* "agar washings" filtrates on the morning of the day before the trial bleeding. On the morning of the trial bleeding the rabbits then receive an intravenous injection of the mixtures to be titrated. The results are read early in the afternoon of the same day. If an adequate antitoxin titer is found, a large bleeding is performed on the same afternoon, i e., about six or eight hours after the trial bleeding.

A sudden rise or drop in concentration of the phenomenon-neutralizing antibodies is a conspicuous feature and may be observed in various periods of uninterrupted immunization. Once a drop occurs, continuation of immunization is frequently valueless. A rest of several weeks or months may reestablish the ability of a horse to produce neutralizing antibodies. After the rest period one or more injections are frequently sufficient to bring about a high concentration of antitoxin, which in turn may promptly drop again after an additional injection. Rises and drops in concentration of the antibodies can be elicited several times in the same horse by alternating periods of immunization with periods of rest. The toxic filtrates alone without the aid of vaccines are capable of stimulating the production of neutralizing antibodies as well as of agglutinins and precipitins.

During several years of experimental immunization of horses phenomenon-neutralizing antibodies of numerous batches of serum were tested against toxic substances derived from various strains of *B typhosus* and also derived from rough and smooth variants. The results reported previously<sup>23</sup> can be summarized as follows. Various stock strains of *B typhosus* were found to produce reacting factors (toxins) which differed in their neutralizability by antistock immune horse serums. Of four stock strains chosen for this work, two occupied extreme positions. One showed a high degree of neutralizability with serums that were strain homologous and strain heterologous. Another strain showed only irregular neutralizations with the same serums. The remaining two stock strains occupied intermediate positions in the degree of consistent neutralization. Toxic substances derived from rough variants of *B typhosus* were not neutralized by antistock serum but acquired a new antigenic specificity. It was found also that cultivation of *B typhosus* strains on human blood produced important changes in the neutralizability of *B typhosus* toxic substances.

In developing the antityphoid serum it seemed important, therefore, to employ toxic substances derived from strains of various neutralizability as well as toxic substances derived from strains of *B typhosus* cultured on human blood. Toxic substances derived from rough variants also were employed, because the formation of rough variants may be expected in vivo in the course of an infectious disease of prolonged duration, such as typhoid. For these reasons polyvalent filtrates and vaccines consisting of toxic substances derived from various strains and variants were used for the immunization of the horses. Incidentally, it should be mentioned that the employment of strains grown on human blood broth brought about the formation of antihuman serum precipitins.

*Titration of B Typhosus Toxins*—The rabbits used for titrations were each given an intradermal injection of 0.25 cc of undiluted *B typhosus* "agar washings" filtrate. The animals were divided into groups of three. Twenty-four hours later a single intravenous injection of the filtrate, diluted in an 0.85 per cent solution of sodium chloride, was given to each rabbit. The dose was 1 cc per kilogram of body weight. Each group of rabbits received intravenously a

different dilution of the filtrate. The local reactions were read four or five hours after the intravenous injections were given. The titrations were carried until the lowest dilution was found which gave no reaction in the three rabbits tested, as well as the highest dilution which gave reactions in one or more rabbits of the group. The minimal dose of the toxin was then considered as lying between these two figures. If a given filtrate was employed for any length of time, repeated control titrations were made. In these control tests the dilutions employed were both the highest dilution capable of eliciting a reaction and the lowest dilution giving no reaction. This was necessary since a loss of potency occurred during storage of the filtrates, as well as an occasional increase of the potency.

*Titration of Serum Neutralization of B Typhosus Toxins*—Into an area on the skin of the abdominal wall of a rabbit was injected 0.25 cc of the undiluted filtrate. From twenty-two to twenty-four hours later a single intravenous injection was given of a mixture of the same filtrate (diluted previously in an 0.85 per cent solution of sodium chloride to the desired degree) with undiluted horse serum in the proportion of four to one. The mixtures prepared on the morning of the experiments were incubated in a water bath at 37.5 C for one hour. The precipitate in the mixture was broken up by shaking immediately before the injection. The intravenous dose of the mixture was 1.25 cc per kilogram of body weight. The readings of the reactions were made four or five hours after the intravenous injection. Each mixture was tested in three rabbits. If no reactions were obtained in the three rabbits tested, the result was considered as showing complete neutralization of the toxin. If one or two of the three rabbits tested showed reactions, the result was recorded as showing irregular neutralization.

Thus, the maximum amount of reacting factors completely neutralized by 0.25 cc of a given serum was used to compute the neutralizing titer. As was noted in the experiments described, a constant amount of serum was titrated against increasing amounts of the filtrate. The danger of error arising from possible variations in susceptibility to small amounts of toxins was thus avoided. The neutralization tests proved consistent on repeated reexaminations of the same batches. This has been confirmed by innumerable tests of samples of the serum during the last three years.

The agglutination and precipitation tests were carried out in the usual manner.

#### CLINICAL OBSERVATIONS

Seventy-eight patients with typhoid received from 100 to 500 cc of unconcentrated serum intravenously. If preliminary intradermal or ophthalmic tests revealed definite sensitivity, no serum was given. Each patient received an injection of 10 cc, followed three hours later by 25 cc. If there were no untoward symptoms, 50 cc was given slowly by the intravenous drip method. Either of these procedures was repeated at intervals of from four to eight hours with similar amounts until the total dose was introduced. The usual complications of intravenous serum therapy were encountered and are reported in detail later in the paper. The results of observations with the antityphoid serum are summarized in the accompanying table.

*Effect on Toxemia*—Thirty-nine, or 50 per cent, of the patients showed relief from toxemia following the injection of the serum. In



# Data on the Effect of Antityphoid Antitoxic Serum on Typhoid

Name	Diagnosis*	Duration of Temperature, Days	Serum Given, Day of Disease	Effect of Serum on Temperature†	Serum Sickness‡	Toxicemia§	Comment
L K	3, 2	47	11	0	++	+	Relapse two weeks later
L R	3, 2	39	11	0	+	0	
F A	3, 2	93	21	0	0	+	Otitis media and ethmoiditis
P L	3, 2	38	7	0	+	+	
M F	3, 2	30	13	0	++	+	
L T	3, 2	44	18	0	A++	+	
A N	3, 2	33	9	+	++	+	
L R	3, 2	48	12	+	A	+	Cholecystitis
C A	3, 2	47	21	0	++	+	
J M	3, 2	38	9	0	++ (2)	+	
G G	3, 2	36	8	+	++	+	
M G	3, 2	34	13	+	A+	+	
J K	3, 2	39	10	?	++	+	Low grade fever apparently associated with pyelitis
C A	3	43	18	?	++	+	
L E	2, 3	21	11	?	++	+	Clinically typhoid, no laboratory data
M B	3, 2	40	10	0	+	+	First treated with normal horse, later with immune serum
C W	3, 2	50	15	0	+	+	
E S	3, 2	40	17	0	+	0	
H L	3, 2	50	13	0	+	++	
O C	3, 2	30	22	+	+	+	
G W	3, 2	23	9	+	++	+	Died of perforation during convalescence
C R	3, 2	26	14	+	++	+	
C B	3, 2	20	10	+	+	+	
M S	3, 2	18	10	+	++	++	
H J	3, 2	27	20	+	+	+	
B R	3	21?	7	+	++	+	Case described in text
B S	3, 2	21	16	+	0	+	
R W	3, 2	34	12	+	+	+	
B K	3, 2	43	10	+	++	+	
R S	3, 2	27	13	+	++	?	
S P	3, 2	19	11	+	0	+	Typhoid relapse on the 36th day followed by measles
T G	3, 2	45	7	+	+	+	
M D	3, 4	22	11	+	+	+	
C C	3	20	9	+	+	+	
J M	3	23	9	+	+	+	
J P	2, 3	21	8	+	+	+	Profuse intestinal bleeding stopped a few hours after administration of serum
W H	3, 4	19	15	+	0	+	
J W	3	25	18	+	+	+	Clinically unquestionable typhoid, no laboratory data disappeared a few hours after administration of serum
O M	3	26	10	+	+	?	Clinically unquestionable typhoid, no clinical data
L C	3, 2	46	9	0	++	0	Serum of low potency
J B	3, 2	36	14	+	+	?	
N C	3, 2	43	12	0	+	?	Complicated by measles
B F	3	43	18	+	0	?	
M W	3, 2	109	11	+	0	+	Mild case from onset
J Y	2, 3	43	13	0	+	0	
E E	3, 2	53	9	0	(4 times) ++	?	Relapse on 42d day
G A	3, 2	43	12	0	+	?	
M C	3, 2	45	12	?	(several) +	?	Pneumonia and acute rheumatic endocarditis, died
D K	3, 2	14	11	?	?	?	
J P	3, 2	31	17	+	+	0	Serum discontinued and started again 12 days later when patient was moribund, died
C S	3, 2	30	16	?	+	0	Low grade fever between 32d and 60th day
S M	3, 2	50	13	0	0	+	
L	3	60	25	0	+	+	Died of pneumonia, lower lobes of both lungs
A C	3, 2	21	17	?	?	0	

\* 2 indicates positive blood culture, 3, clinically positive typhoid, and 4, stool positive for B typhosus  
† 0 indicates no effect, ?, unfavorable effect, and +, favorable effect  
‡ 0 indicates no serum sickness, ?, moderate, +, severe, and ++, immediate anaphylaxis  
§ 0 indicates no effect, ?, questionable effect, +, favorable effect, and ++ very favorable effect

Name	Diagnosis	Duration of Temperature, Days	Serum Given, Day of Disease	Effect of Serum on Temperature	Serum Sickness	Toxemia	Comment
E B	3, 2	35	10	0	+	0	Early preparation of serum of low potency
G K	3, 2	61	17	0	+	0	Early preparation of serum of low potency
S O	3, 2	45	37	—	++ (19th)	0	
H R	3, 2	59	15	0	+	0	Early preparation of serum of low potency
W W	3, 2	40	16	0	+	(22d)	0
R H	3, 2	7	6	—	++	0	Died
F M	3, 2	35	12	0	A++	0	30 cc of serum of low potency
L S	3, 2	37	14	0	+	0	
J R	3, 2	81	20	0	0	0	
H W	3, 2	28	9	0	0	0	Early preparation of serum of low potency
F A	3, 2	37	14	0	+	0	Small amount of serum, early preparation of serum of low potency
F M	3, 2	54	15	0	?	0	
V G	3, 2	34	13	0	+	0	
O C	3, 2	57	10	0	0	0	
W B	3	40	7	0	+	0	
V C	3, 2	41	13	0	+	(2)	0
C L	3, 2	60	22	0	0	0	
A P	3, 2	43	13	0	+	0	
F R	3, 2	45	12	0	+	0	
A P	3, 2	9	8	—	0	0	
G D	3, 2	42	10	0	+	0	Bronehopneumonia, died
S W	3, 2	28	12	0	+	0	
G G	3, 2	?	9	0	+	0	Bronehopneumonia, died
S H	3, 2	45	8	0	0	0	Cholecystitis after 20th day
F G	3	22	14	0	++	0	In spite of some relief effect reported questionable because only 50 cc of serum was given

some of the cases this effect was dramatic, a patient who had been in a low muttering, delirious state, with incontinence of stools, would be sitting up in bed and looking and acting as if he were not sick forty-eight hours after the administration of serum. In thirty-two cases the serum had no effect on the toxemia, and in seven the effect was so slight as to be questionable.

*Effect on the Duration of the Disease*—An exact statement as to the duration of fever in any given case presents many difficulties. The history was often vague as to the date of onset, the clinical picture was frequently obscured by fever due to complications, intercurrent infection or serum sickness. Fifty-six of the patients who received serum treatment showed a rise in temperature for over thirty days. In twenty-two cases the duration was less than thirty days.

*Effect on the Temperature*—Twenty-five patients showed a mean fall in temperature following the injection of serum. In some of these cases the fall followed so promptly the giving of serum and occurred so early in the disease that we feel that the serum may have played the important part. In some cases the fall in temperature occurred at the time when defervescence normally begins, and the part played by the serum is discounted.

The records of the temperature in three of the cases illustrate the sudden and dramatic change in the disease in these cases and the totally unexpected end of the disease within a few days.

CASE 1—This patient seemed to be dying. He was in an extremely toxic state, was constantly delirious and disoriented and made involuntary motions. Blood culture showed B typhosus. The spleen was palpable, and there was pronounced leukopenia. From the eighth to the tenth day of the illness 102 cc of

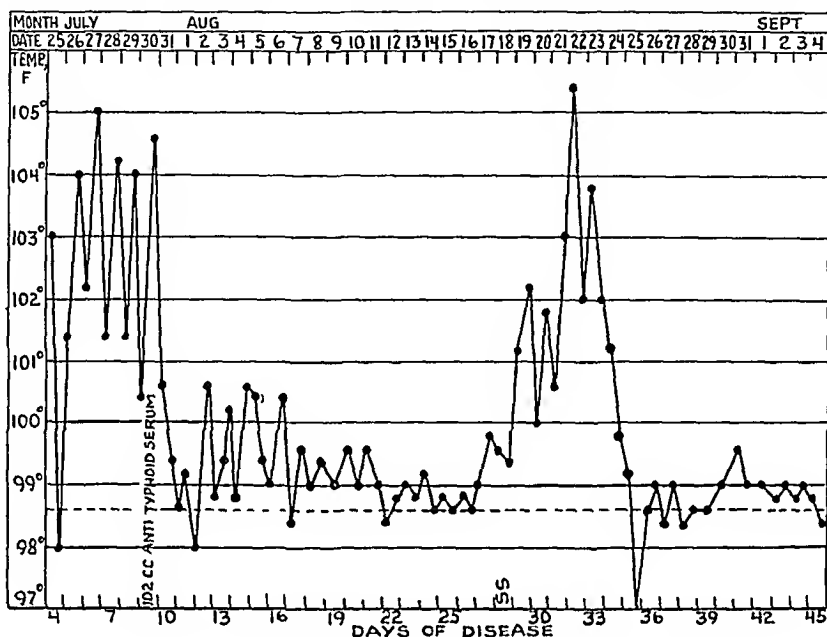


Chart 1—Data on the temperature in case 1

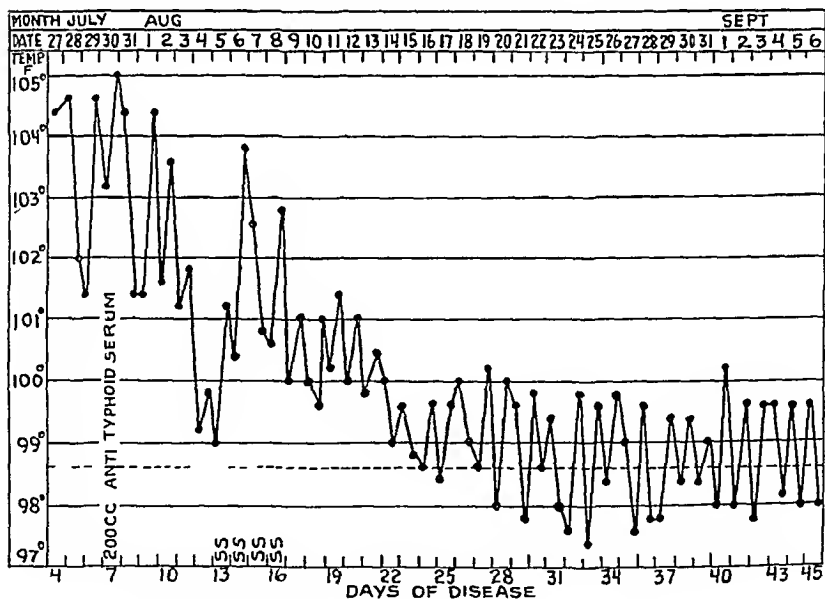


Chart 2—Data on the temperature in case 2

serum was given. A most dramatic effect was noted on the fever. The temperature fell to normal, and the disease apparently terminated on the eleventh day. Blood cultures were repeatedly sterile thereafter. Although all other clinical manifestations of typhoid disappeared, a postinfectious psychosis persisted, in spite of a normal temperature for three weeks after the end of the disease.

CASE 2—This patient was admitted to the hospital on the third day of the disease. She was in a moderately toxic state. The temperature reached 104.6 or 105 F daily. A total of 200 cc of antityphoid serum was administered on the sixth and seventh days of the disease. On the eighth day the patient appeared less drowsy, on the ninth day the temperature began to drop and was normal on the eleventh day of the disease. Serum sickness developed six days after the injection of serum, and was marked by fever, urticaria and polyarthrititis which persisted for three days. The agglutination titers (Widal tests), which showed negative results before the injection of serum, were 1:1,280 on the eighth, ninth and twelfth days of the disease, dropped to 1:320 on the thirty-third day of the disease and subsequently became negative again.

CASE 3—This patient was admitted on the sixth day of illness. He was acutely ill and in a typhoidal and moderately toxic state. The temperature ranged between 100.4 and 106 F during the three days before serum was administered. A total of 485 cc of antityphoid serum was injected intravenously during fifteen

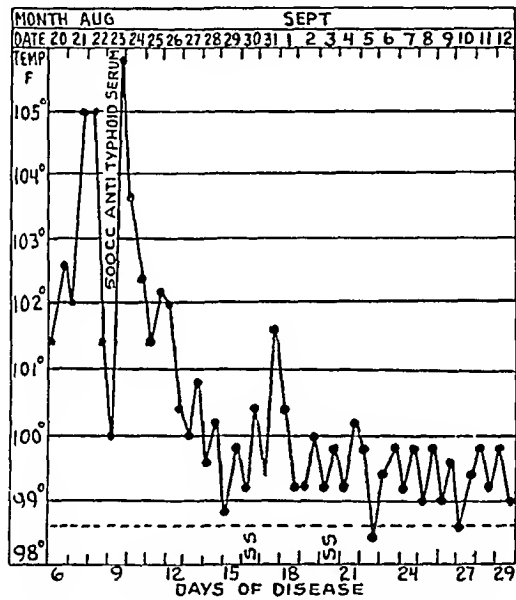


Chart 3—Data on the temperature in case 3

and one-half hours. Within twenty-four hours following the injection of the serum the temperature dropped to normal (i.e., on the twelfth day of the disease) and remained normal thereafter, with the exception of a peaklike rise to 101.8 F on the afternoon of the eighth day after the last injection of serum. The rise was coincident with the development of serum sickness, which manifested itself in urticaria and pruritus.

Twenty-four hours after the injection of serum, i.e., on the tenth day of illness, the Widal test, which had previously shown negative results, reached a titer of 1:320.

*Serum Sickness*—Facilities for the concentration of the antityphoid antitoxic serum were not readily available. It was necessary, therefore, to employ large quantities of unconcentrated serum. The intravenous injection of such large quantities of horse serum resulted in the subsequent development of clinical manifestations of serum sickness in a large proportion of the cases.

The first manifestations of serum sickness began, as a rule, on or about the sixth day after the first injection. The symptoms in order of frequency were fever, urticaria, tachycardia and arthralgia. The serum sickness persisted for from two to five days. It showed a tendency to recur on or about the twelfth or the fourteenth day and again from the eighteenth to the twenty-first day after the injection was given. The second and third recurrences were sometimes more severe than the primary attack.

The symptoms of serum sickness were seldom alarming, but they brought discomfort to the patient and often obscured the clinical picture during the stage of recovery. The fever which usually accompanied the serum sickness frequently made it difficult or impossible to interpret the influence of the therapeutic serum on the temperature curve of

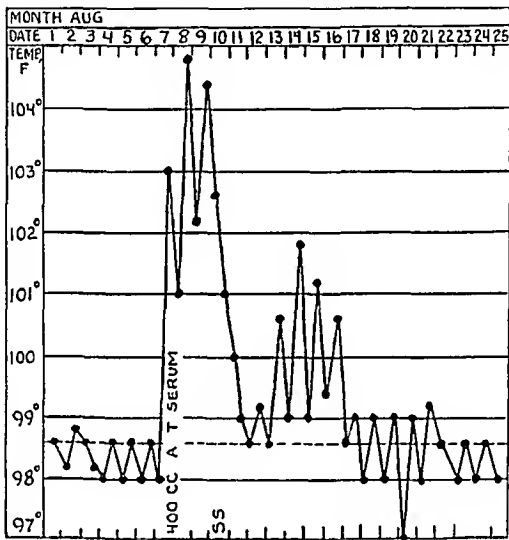


Chart 4—Data on the temperature in a normal volunteer

typhoid. This is illustrated by the accompanying temperature curve (chart 4) of a normal, afebrile volunteer who received an intravenous injection of 400 cc of antityphoid horse serum.

As seen in this instance, there was an immediate rise in temperature to 104.8 F following the injection of the serum. The temperature remained approximately at that level for the next twenty-four hours and then sharply dropped to normal within the second twenty-four hours. On the fifth day after the injection of serum typical manifestations of serum sickness developed, with the temperature fluctuating between 99 and 101.8 F, and the symptoms persisted for several days, until the temperature again became normal.

The occurrence of similar febrile periods of serum sickness following the injection of antitoxic antityphoid serum into patients with typhoid may have served to prolong the elevation of temperature and to obscure an otherwise obvious influence of the serum on the toxic manifestations of the illness and on the duration of the disease.

Fourteen patients showed no bad effect of any sort, thirty-nine had mild serum sickness, and twenty-two had severe serum sickness, i e, a sharp rise in temperature, urticaria and arthralgia. Three patients had anaphylactic shock. Four patients had two attacks of serum sickness, and one patient had four.

*Effect of Serum on Agglutinins for B Typhosus*—In forty-seven cases Widal titiations were made shortly before the administration of serum, from one to three days after the injections were completed and frequently at short intervals until the patient was discharged. The analysis of the data obtained is as follows:

Twenty-two patients showed a marked rise in the agglutination titer which was unquestionably due to the injection of serum. In eighteen of these cases the Widal titer, which had been recorded previously as negative or in the range between 1:80 to 1:160, reached a titer of 1:1,280 within twenty-four hours after the administration of the serum. In three cases it reached a titer of 1:25,600, in another 1:10,000. In ten other cases there was a rise in titer up to a dilution of 1:640 following the administration of serum.

These results can be interpreted as being due to the injected serum, for the rise in the Widal titer occurred in the early stages of the disease immediately after the injection of the serum and in titers well above normal expectancy for the given stages of the disease. In four cases there was a doubtful effect of the serum on the agglutination titer, and in eleven cases no effect was observed.

Because of the small number of cases in each group it seemed to be difficult to draw any conclusions as to the correlation between the rise of the Widal titer following administration of serum and the therapeutic effect.

*Effect on Bacteremia*—In twenty-two of the forty-two cases in which an unquestionable effect of the therapeutic serum on the toxic manifestations of the disease was noted the positive blood culture became sterile within forty-eight to seventy-two hours after the administration of the serum. Sterile blood cultures were also noted after the administration of serum in twelve cases of demonstrable bacteremia in which there was a moderate effect of the serum. In other words, the bacteremia cleared up within a few days after treatment with serum in thirty-four cases. In contrast to this result, the following case must be reported as unusual in our experience:

CASE 4—This girl was given 400 cc of serum between the fourteenth and the eighteenth day of illness because she was in a toxic and typhoidal state. The clinical picture changed within twenty-four hours, and at the end of forty-eight hours she was normally active, looked entirely well and had a good appetite. The temperature began to fall within twenty-four hours after the serum was administered and reached normal three days later. From that time on the temperature

remained normal, and the patient felt well. To our surprise, blood cultures taken on the fourth, eighth and tenth days of normal temperature showed B typhosus, although clinically the patient was no longer suffering from typhoid or from any typhoidal complications. The first negative blood culture was obtained on the fourteenth day of normal temperature.

In this one instance B typhosus bacteremia persisted for at least ten days after all the toxic manifestations of typhoid had apparently been completely neutralized by the antitoxin and the patient was clinically well.

*Mortality*—In seventy-eight cases in which serum was administered there were seven deaths—a mortality of 8.9 per cent. One of the

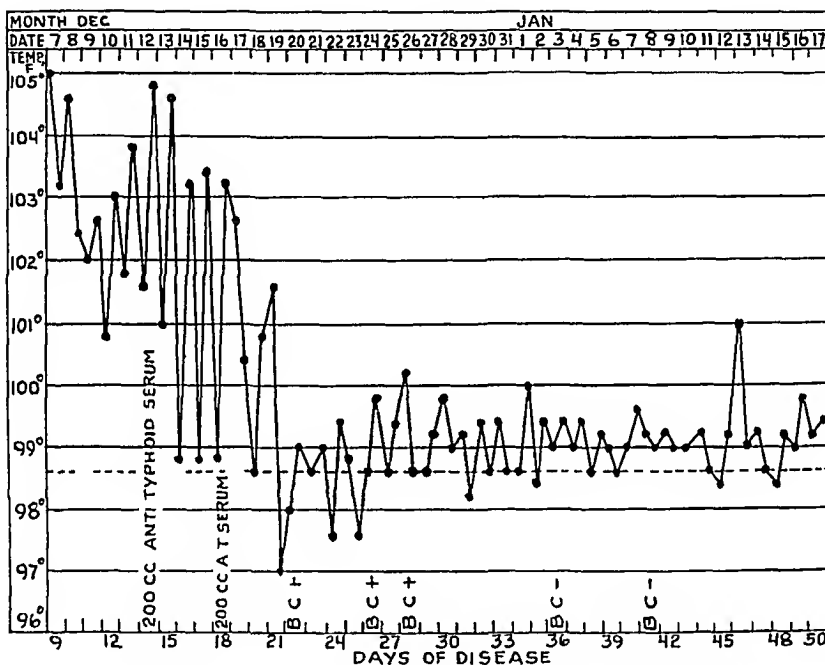


Chart 5—Data on the temperature in case 4

patients was moribund when serum was given, two died of pneumonia (one in thirty-six hours and one after an interval of two weeks) and one died of toxemia twelve hours after the serum was injected.

*Controls*—A control series of patients with typhoid was studied in which equally large amounts of normal horse serum were used. Four of the seven persons so treated died—a mortality of 57 per cent. One patient was distinctly harmed by serum, two probably were harmed and one was distinctly benefited. That the results would be more valuable if an equal number of controls were used is unquestioned, but the high mortality among the controls following the administration of large quantities of normal horse serum definitely prohibited this procedure. The records of the Charity Hospital, New Orleans, for a period of three years, including the year of our work there, were collected and analyzed as a rough

control There were two hundred and fifty-six cases of typhoid with fifty-six deaths—a mortality of just over 22 per cent In 40 per cent of the cases the duration of fever was less than thirty days The average duration of fever was thirty-eight days for this group Among the patients who were given serum treatment the mortality was 8.9 per cent, 35 per cent had a duration of fever of less than thirty days, the average duration, including serum sickness, being thirty-eight days

#### COMMENT

The average duration of fever and the percentage of cases in which the duration was less than thirty days when serum was administered are roughly identical with the results in the control series The mortality of 9 per cent as against 22 per cent probably means little in a small number of cases

Taking into consideration all the various effects, we are of the opinion that sixteen patients showed a definitely favorable effect, i.e., relief from toxemia, a fall in the mean temperature and a shortened duration of the disease, without any bad effects, such as serum sickness These sixteen patients represented roughly 20 per cent of the total number who received serum treatment In the series of patients treated with normal horse serum one patient in seven showed a distinctly favorable effect—14.3 per cent, which does not indicate a wide difference in a small series

The high incidence of serum sickness with its added discomfort to the patient suffering from long-continued fever makes the use of unconcentrated serum unacceptable for general use One of us (G. S.) is now working on the problem of making a more concentrated polyvalent serum

As will be seen, our figures do not justify the assumption of any very remarkable result Against this, we have often obtained the distinct clinical impression that marked relief from toxemia resulted in certain of the cases This change must be observed to be appreciated, and it is the only thing on which we base our hopes for further treatment along this line

In conclusion we wish to state that the work reported is of a purely experimental nature and that the serum in its present form is not advocated for general therapeutic use The report is made in order to bring out the possible beneficial effects of an antityphoid antitoxic serum, the preparation of which is made possible by the development of the phenomenon of local cutaneous reactivity to bacterial filtrates



# ALTERNATION OF THE HEART SOUNDS

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Volhard <sup>1</sup> in 1905 studied the characteristic sphygmographic features in cases of pulsus alternans and reported that by listening to the heart one could recognize a conspicuous alternation of the second heart sound in all the cardiac cycles and of the first heart sound in only three or four cycles after each extrasystole. This alternation of the sounds revealed itself through modifications in their intensity and pitch, the sounds in the cycle with a large pulse beat were more intense and of a higher pitch than those in the cycle with a small pulse beat.

Although the initial fact was verified at the beginning of the present century, there are only a few cases reported in the medical literature in which alternation of the heart sounds was recognized on auscultation (Meyer and Levy <sup>2</sup> and Morris <sup>3</sup>). With the exception of Morris, <sup>3</sup> all other authors who have been interested in alternation of the heart sounds as a manifestation of alternation of the heart beats (Wenckebach and Winterberg, <sup>4</sup> Mackenzie, <sup>5</sup> Lian, <sup>6</sup> Laubry, <sup>7</sup> Clerc <sup>8</sup> and Edens <sup>9</sup>) expressed the opinion that alternation of the heart sounds is exceptional.

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1 Volhard, F. Ueber den Pulsus alternans und pseudoalternans, *Munchen med Wchnschr* **7** 590, 1905

2 Meyer, A., and Levy, R. Un cas de pouls alternant sans hypertension et avec alternance des bruits du cœur, *Presse med* **32** 131, 1924

3 Morris, R. A. The Clinical Recognition of Pulsus Alternans, *J. A. M. A* **87** 463 (Aug. 14) 1926

4 Wenckebach, K., and Winterberg, H. Die Unregelmässige Herztätigkeit, Leipzig, Wilhelm Engelmann, 1927

5 Mackenzie, J. Les maladies du cœur, Paris, Felix Alcan 1920

6 Lian, C. Aparato circulatorio, in *Tratado de patologia medica*, Barcelona, Editorial Pubul, 1924

7 Laubry, C. Maladies du cœur et des vaisseaux. Nouveau traite de pathologie interne, Paris, Gaston Doin, 1930

8 Clerc, A., and Deschamps, N. Cœur et vaisseaux, Paris, Masson & Cie, 1931

9 Edens, E. Die Krankheiten des Herzens und der Gefasse, Berlin, Julius Springer, 1929

and is likely to be found only in rare cases of alternation of the pulse beats of unusually high degree

Convinced that "method is all in the progress of science," we studied the quality of the sounds in patients with alternation of the heart sounds, using for this purpose phonocardiographic records—a method that we consider trustworthy

Kahn<sup>10</sup> in 1911 had already taken advantage of the use of a record of the heart sounds as a means of studying certain facts in circulatory dynamics in alternation of the heart beats experimentally produced in animals by the injection of glyoxylic acid. The goal of this author differed from our own, also, the conditions of his experiments (exposed heart) were different

#### MATERIAL AND METHOD

For our study we employed seven patients with pulsus alternans. In six (cases 1, 2, 3, 4, 5 and 6) the alternation was independent of respiration, and in the other patient (case 7) it was related to respiration, the respiratory rate being nearly

#### *Summary of Data on Patients with Alternation of the Pulse Beats*

Case Number	Heart Rate	Breathing Movement	Degree of Alternation of Pulse	Strong Contraction						Weak Contraction					
				First Heart Sound	Second Heart Sound	Duration of Systole, Seconds	Delay of the Pulse Wave, Seconds	QRS Complex	T Wave	First Heart Sound	Second Heart Sound	Duration of Systole, Seconds	Delay of the Pulse Wave, Seconds	QRS Complex	T Wave
1	111	32	High	Strong		24	16	Small	Large	Weak		22	18	Large	Small
2	115	30	High	Strong	Weak	24	16			Weak	Strong	24	18		
3	93	29	High	Strong	Weak	28	16			Weak	Strong	27	18		
4	112	23	Slight	Strong	Strong	24	16			Weak	Weak	24	16		
5	187	29	High	Strong	Weak	?	16		Large	Weak	Strong	?	16		Small
6	107	25	Mild	Strong		26	16			Weak		25	16		
7	40	19	Mild	Strong		36	16			Weak		36	16		

one-half the heart rate. In the first six patients the alternation persisted and was even more conspicuous with voluntary retention of respiration, in the other patient, alternation disappeared with voluntary suspension of respiration.

The six patients with true alternation of the heart beats presented the following conditions: ventricular paroxysmal tachycardia (case 5), syphilitic aortic incompetence (case 3), cardiac enlargement with arterial hypotension and heart failure (case 4), coronary arteriosclerosis (case 1) and high arterial pressure with heart failure (cases 2 and 6).

The only patient (case 7) with alternation of the pulse beat which was related to respiration had a permanent nodal rhythm, the heart rate was usually about 40 per minute and the respiratory rate about 19 per minute.

<sup>10</sup> Kahn, R. H. Studien am Phonokardiogramme, Arch f d ges Physiol 140 471, 1911

The degree and intensity of the alternation were not equal in the seven cases and may be divided into three groups, according to the classification of White<sup>11</sup> and Morris<sup>3</sup>

The alternation was of high degree in four cases (1, 2, 3 and 5) and could be detected easily by feeling the radial pulse. The alternation was of mild degree in two cases (4 and 7), and feeling the pulse was inadequate for its recognition, although it was recorded in the sphygmogram. The alternation was slight in the remaining case (6). It was impossible to detect the regular change in the amplitude of the pulse beats in this case by merely feeling the pulse, and it could not be recorded in the sphygmogram. It could be recognized only by listening to the arterial sound through a stethoscope placed over the brachial artery at the elbow under an inflated rubber cuff, the pressure of which was slightly inferior to the systolic pressure in the artery (fig 1).

In each of the seven cases a record was obtained of the heart sounds, Frank's segmentary capsule, with the modifications introduced by Wiggers and Dean,<sup>12</sup> being used. The record was obtained with the receiver placed in the precordial region where a previous examination had revealed heart sounds of the greatest intensity. The patients were told to breathe slowly and then to interrupt their breathing in the expiratory phase, an interruption that was always of slight duration owing to the circulatory condition. Electrocardiographic and sphygmographic records were obtained simultaneously with the record of the heart sounds. For the electrocardiograms, an Einthoven electrocardiograph of standard type was used, and for the sphygmograms, an oscillographic Boulitte tambour. In four cases (1, 2, 3 and 4), simultaneously with the phonocardiogram, a phlebogram was obtained by means of Frank's segmentary tambour, in one case (7) a pneumogram was also made.

In the cases in which the alternation could be detected only by listening to the arterial sounds through a stethoscope placed below the inflated cuff, a graphic record of these sounds was obtained simultaneously with the other records. This was done by putting the receiver at the elbow on the brachial artery.

Before all these tracings were secured, complete clinical, roentgenographic and electrocardiographic observations were made on each patient.

The auscultatory findings were carefully checked by various expert observers for the purpose of excluding personal errors.

## RESULTS

*Phonocardiogram*—The series of groups of oscillations produced by the first heart sound showed an alternation in their height and size in each of the records obtained in the seven cases (figs 2, 3, 4 and 5). A cardiac cycle with a strong first sound was followed by a cycle with a weak first sound and so on through many cycles. The difference in the size of the oscillations produced by a strong first sound and those produced by a weak first sound in two consecutive cycles varied greatly in the seven cases. In certain cases the difference was reduced to a minimum, as in cases 2 and 6 in which the oscillations produced by a weak first sound were nearly nine-tenths the size of those produced by a strong first sound. In the other cases (1 and 4) the difference was conspicuous, the oscillations

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11 White, P. D. Alternation of the Pulse. A Common Clinical Condition, *Am J M Sc* **150** 82, 1915.

12 Wiggers, C. J., and Dean, H. The Principles and Practice of Registering Heart Sounds by Direct Methods, *Am J M Sc* **153** 666, 1917.

produced by a weak first sound were two-thirds the size of those produced by a strong first sound. In the remaining cases, those produced by a weak first sound were three-fourths (cases 3 and 5) and four-fifths (case 7) the size of the corresponding oscillations produced by a strong first sound.

The duration and the number of double oscillations were the same for the strong first sound as for the weak first sound in five cases (3, 4, 5, 6 and 7). In the other two cases the group of oscillations for a weak first sound was wider, that is, the sounds were of longer duration and were formed by a double oscillation more than the group for the strong first sound in the same record.

The series of groups of oscillations produced by the second heart sound had an alternating height in four of the seven cases (2, 3, 4 and 5). The analysis of the phonocardiographic records made in these four cases showed that a cycle with a strong second sound was followed by a cycle with a weak second sound and so on for many cycles. The difference between the size of the large and that of the small oscillations produced by the second sounds in two consecutive cycles was evident. The small oscillations were three-fourths the size of the large oscillations in case 3, two-thirds the size in cases 4 and 5 and one-half the size in case 2.

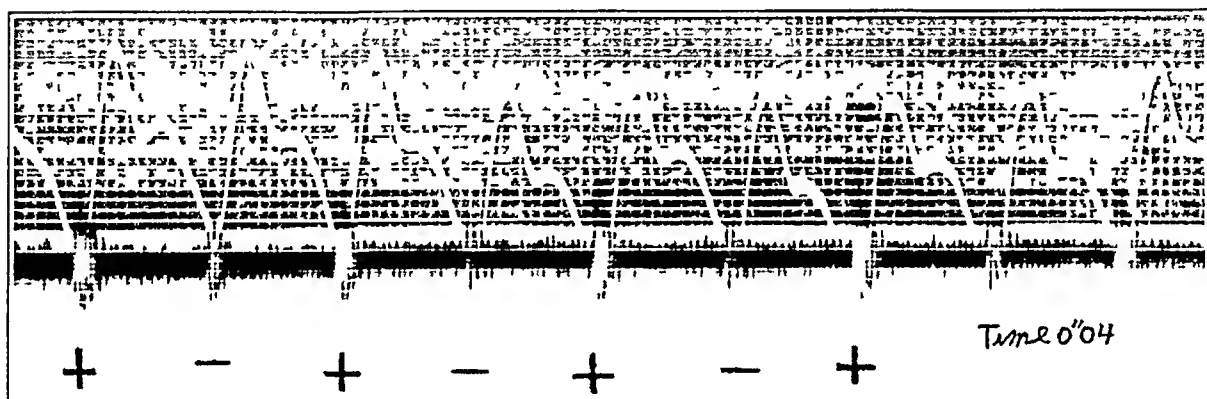


Fig 1—While the sphygmogram (upper section) does not show an alternation of the pulse waves, the record of the arterial sounds (lower section) shows the regular succession of a strong (+) and a weak (—) sound. The difference in the height of the pulse wave is due to breathing movement. Time, 0.04 second.

The duration, or width, of the group of large oscillations produced by the second sound was the same as that of the small oscillations of the following cycle in the four cases in which the alternation of the second sound could be detected on the graphic records. The number of double oscillations remained equally unaltered for both the strong and the weak second sounds in the four cases in which alternation in the amplitude or size of the oscillations was present.

In the four cases (2, 3, 4 and 5) in which there coexisted an alternation of the first sound with an alternation of the second sound, the alternation was discordant for the same cycle in three cases (2, 3 and 5) and concordant in the remaining case (4). In the graphic records obtained in three cases in which there was discordant or opposite alternation of the heart sounds, an analysis revealed the following facts. The cycle with a strong first sound had a weak second sound, and the cycle with a weak first sound had a strong second sound (figs 3 and 5).

In the case in which a double alternation of the sounds was concordant in the same cycle, a strong first sound occurred with a strong second sound and a weak first sound with a weak second sound (fig 2)

In four cases the interval between the beginning of the first sound and the beginning of the second sound was the same in the cycle with a strong first sound as in the cycle with a weak first sound. In the remaining three cases (1, 3 and 5) the interval was greater in the cycle with a strong first sound than in the one with a weak first sound.

*Sphygmogram and Phonocardiogram*—The sphygmograms made in six cases, (1, 2, 3, 4, 5 and 7) showed the succession of a large pulse wave and a small pulse wave. In the other case (6) this succession of alternate large and small waves could be detected only by listening to the artery in the elbow and by obtaining a graphic record of the arterial sounds at this place (fig 1)

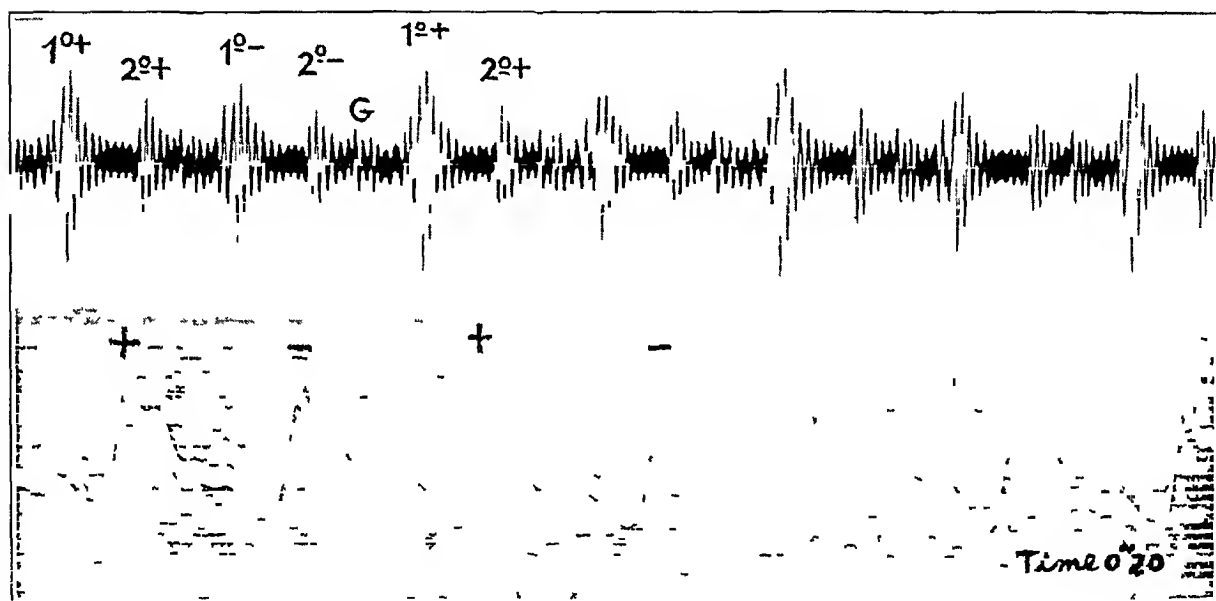


Fig 2—Alternation of the pulse beats (lower section) and of the heart sounds (upper section). The cardiac cycle that produces a large pulse wave (+) has both strong first sounds ( $1^{\circ}+$ ) and strong second sounds ( $2^{\circ}+$ ), that is, there is concordant alternation between the pulse beats and both heart sounds. G indicates protodiastolic gallop rhythm. Time, 20 seconds.

The interval between the large pulse wave and the small pulse wave that follows was equal to that between the small pulse wave and the following large pulse wave in four cases (4, 5, 6 and 7). In the three other cases (1, 2 and 3) the interval between the large and the small pulse wave was greater than that between the small and the following large pulse wave.

The sphygmogram made simultaneously with the record of the heard sounds in the seven cases showed that the strong pulse wave in the sphygmogram corresponded to the cycle with a strong first sound and, in the same way, that the small pulse wave corresponded to the cycle with a weak first sound. The correlation of the pulse waves with the alternation of second sounds that existed in four cases (2, 3, 4 and 5) was equal to that of the pulse waves with the first sounds in only one case. In the remaining cases the correlation was reversed, that is, a

large pulse wave corresponded with the cycle with a weak second sound and a small pulse wave corresponded with the cycle with a strong second sound (figs 2 and 3)

The records of the pulse beats and the heart sounds made simultaneously revealed also the following facts. The delay in the appearance of large and small pulse waves, that is, the interval of time between the beginning of the first heart sound and the production of the pulse wave, was the same in four cases (4, 5, 6 and 7). The delay in the appearance of the small pulse wave was more conspicuous than that of the large wave in the three remaining cases (1, 2 and 3).

*Electrocardiogram and Phonocardiogram*—The electrocardiogram showed an alternation of its complexes in only two of the seven cases (1 and 5). This alter-

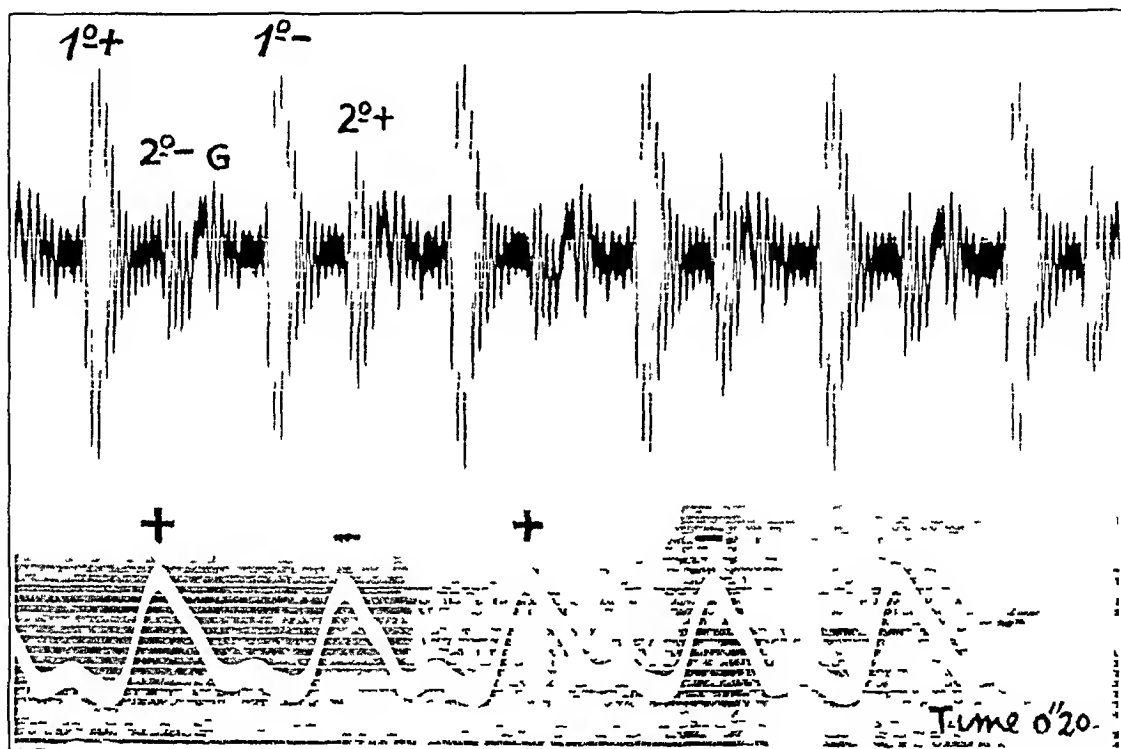


Fig 3—Alternation of the pulse beats (lower section) and of the heart sounds (upper section). The cardiac cycle that produces a large wave ( $+$ ) shows a strong first sound ( $1^{\circ}+$ ) and a weak second sound ( $2^{\circ}-$ ), that is, there is concordant alternation between the pulse beat and the first sound and discordant alternation between the pulse beat and the second sound. *G* indicates protodiastolic gallop rhythm. Time, 20 seconds.

nation affected only the T wave in one case (5) and the QRS complex in the other case (1), in the latter there was also a slight alternation of the T wave.

The alternation of the T wave in case 5 could be seen in three or four successive complexes, after that it disappeared for a time, and then appeared again, and so on. The phonocardiogram obtained simultaneously showed alternation in the first and second sounds each time that there was alternation in the T wave in the electrocardiogram. A cycle with a large T wave corresponded to a cycle with a strong first sound and a weak second sound (fig 5).

The alternation of the QRS complex in case 1 was present in the entire record. In this case, a cycle with a large QRS complex corresponded to a cycle with a weak first sound in the simultaneously registered phonocardiogram (fig 4).

*Pneumogram and Phonocardiogram*—In the only case in which the alternation of heart sounds was associated with the respiration, the pneumogram recorded simultaneously with the phonocardiogram showed that the first heart sound was stronger during inspiration and weaker during expiration (fig 6).

*Auscultation*—Listening to the heart revealed alternation of the heart sounds in the seven cases. In four (1, 3, 4 and 7) auscultation revealed alternation of only the first sound. In the other three cases both sounds were alternate. Alternation of the first sound was more easily recognized than alternation of the second sound in case 4, while alternation of the second sound was more conspicuous than alternation of the first sound in the other two cases (2 and 5).

The alternation of the sounds consisted in changes in their intensity and pitch and also in their cadence. After a cycle with an intense, high-pitched, dry sound

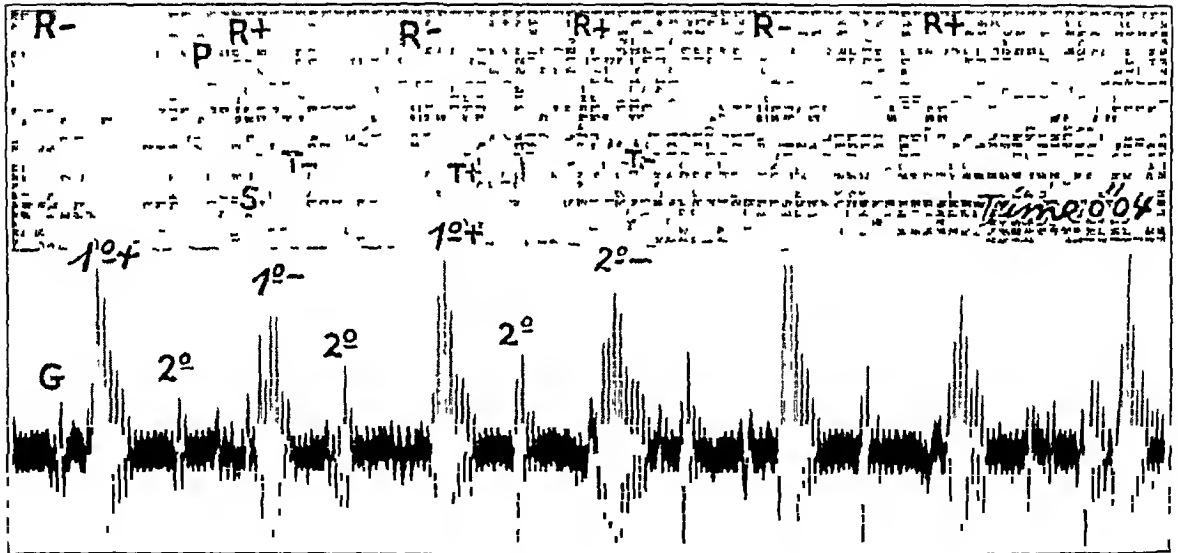


Fig 4—Alternation of the first sound (lower section) and of the QRS complexes (upper section). The cardiac cycle with a strong first sound ( $1^{\circ}+$ ) has a corresponding small QRS complex ( $-$ ), that is, there is discordant alternation between the first sound and the QRS complex. G indicates presystolic gallop rhythm. Time, 0.04 second.

there followed one with a less intense, low-pitched, muffled sound, and so on, giving the sensation that the cycle the first sound of which was less intense was nearer to the sounds of the preceding cycle than to those of the following cycle, instead of being equidistant from both the following and the preceding sound.

To summarize, auscultation revealed alternation in the sounds only at certain moments, at other times it seemed as if the alternation had disappeared completely. During many cycles alternation of the sounds was easily recognized, but during many others it was less conspicuous and in some it seemed to be wholly absent.

Single premature beats were usually followed by conspicuous alternation in the sounds. This change was frequently confined to a few cycles. The alternation was easily recognized during voluntary retention of respiration save when it was associated with the respiratory movements.

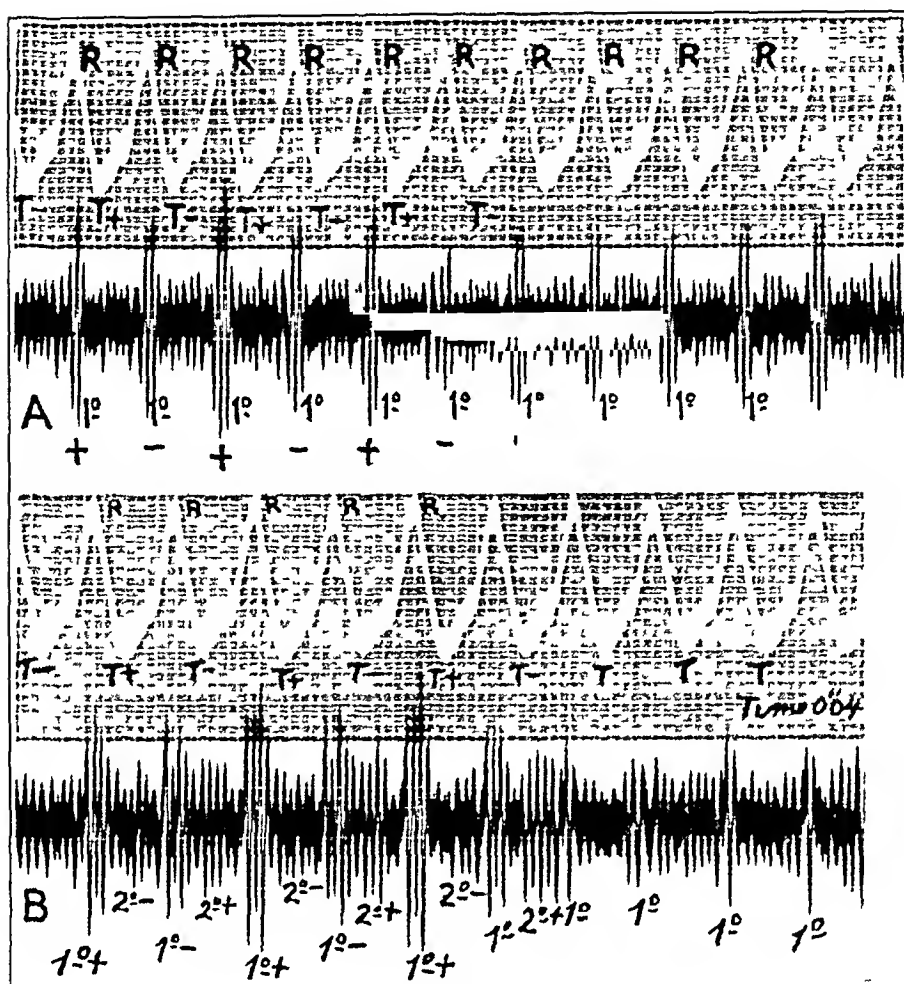


Fig 5—Alternation of the heart sounds (lower sections) and of the T waves (upper sections) in a case of paroxysmal ventricular tachycardia. The cardiac cycle with a large T wave (+) has a strong first sound ( $1^{\circ}+$ ) and a weak second sound ( $2^{\circ}-$ ), that is, there is concordant alternation between the first sound and the T wave and discordant alternation between the second sound and the T wave. A shows the part of the record where the alternation of the first sound is better appreciated. B is another part of the record where the alternation of the second sound is better appreciated. In both parts it may be seen how the alternation of the sounds stops when the alternation of the T wave ceases to produce itself. Time, 0.04 second.

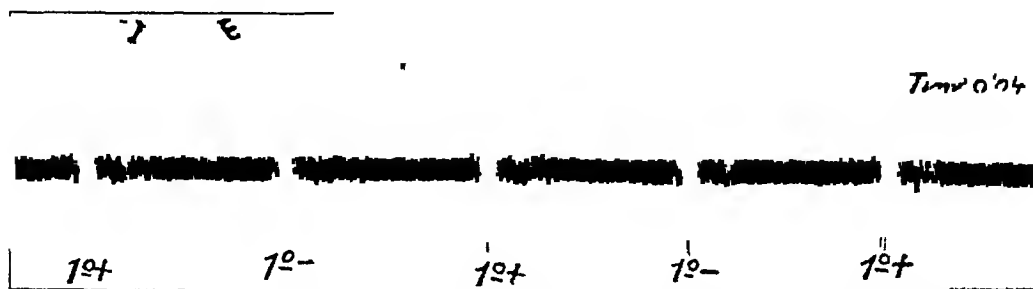


Fig 6—Alternation of the heart sounds (lower section) in relation to breathing movements (upper section). During the inspiration (I) the first sound ( $1^{\circ}+$ ) is strong. Time, 0.04 second.



## COMMENT

Knowledge concerning circulatory dynamics in alternation of the heart has been gained by recording the heart sounds and by obtaining volume and pressure curves on animals in which alternation has been produced by different methods (Kahn,<sup>10</sup> Straub,<sup>13</sup> Wiggers<sup>14</sup>) The pressure curves have revealed the regular occurrence of a cycle with increased systolic intraventricular pressure followed by one with decreased systolic intraventricular pressure The increased pressure produces what is known as a strong heart contraction, while the decreased pressure results in a weak contraction The duration of the systole of a strong contraction is commonly a few hundredths of a second longer than that of a weak contraction The same curves have also shown that the ventricular volume at the end of the systole of a strong contraction is smaller than that at the end of the systole of a weak contraction, that is, the systolic residue of the strong contraction is smaller than that of the weak contraction The large or small quantity of blood thrown into the systemic arteries at every contraction is the cause of successive large and small pulse beats A high pulse wave corresponds to the strong contraction The pulse beats may succeed one another with perfect regularity, or a certain irregularity may be present though the rhythm of the heart remains perfectly regular This irregularity is due to the greater delay of the small wave

The abruptness of the increase in the intraventricular pressure at the beginning of the systole of the strong contraction is the cause of the increased intensity of the first sound as compared with the intensity of the same sound during a weak contraction in which the augmentation of intraventricular pressure is less abrupt Just as a high pulse wave corresponds to a strong contraction, a strong first sound corresponds to a large pulse beat, that is, the alternation of the first sound is concordant with the alternation of the pulse beat The fall of intraventricular pressure at the end of the systole, which is more abrupt in the strong contraction, is the cause of the increase in the intensity of the second sound as compared with the intensity of the same sound in the weak contraction, during which the fall of intraventricular pressure is less sudden Just as a large pulse wave corresponds to a strong contraction, a strong second sound corresponds to a large pulse beat, that is, alternation of the second sound and alternation of the pulse beat are also concordant

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13 Straub, H    *Dynamik des Herzalternans*, *Deutsches Arch f klin Med* **123** 403, 1917

14 Wiggers, C J    *The Dynamics of Ventricular Alternation*, *Ann Clin Med* **5** 1022, 1926

The knowledge of these facts concerning the circulatory dynamics of alternation, discovered by experiments on animals, makes it unnecessary to comment further on the findings in our seven cases of pulsus alternans save as they relate to the alternation of the second sound, which, instead of being concordant, as has been encountered in experiments on animals, was found to be discordant in three of the four cases in which it was present

Before we try to explain the possible causes of this disagreement between clinical and experimental findings, we must face the possibility of an error in the methods utilized by us. The resemblance of our findings to the clinical and experimental findings of others suffices to dismiss such a possibility. This view is strengthened by the following fact. In the only case of alternation of the heart sounds in man that we have found reported in the medical literature (Wiggers<sup>15</sup>), the second sound was discordant in its alternation with the pulse wave. Though the author did not state the fact, the graphic record published in his paper shows clearly that with an intense first heart sound there was a less intense second sound and vice versa. As the alternation of the first sound has until now been considered concordant with that of the pulse beat, alternation of the second sound must be considered discordant.

Considering the dynamic conditions in the strong and weak contractions, we believe that both sounds should be more intense in the strong than in the weak contraction.

Since we do not believe that the second heart sound can be less intense in the strong than in the weak contraction, we are of the opinion that the discordant alternation of the second sound, when compared with the alternation of the pulse beat (verified by ourselves in human beings), can be explained only by an alteration in the conditions that regulate the transmission of heart sounds from their original site to the place in the cardiac area where they are heard.

In a textbook recently written by one of us (C. P.<sup>16</sup>) it is stated that the acoustic phenomena taking place in the valves or in the cavities of the heart themselves reach the ear of the observer or the receiver of the registering apparatus in the following manner. The vibration spreads to the walls of the heart and from there to the thoracic walls.

The transmission of the sound from the heart to the thoracic walls takes place because of the intimate relation between the two, for the pulmonary tissue is a bad conductor of sound, that is, the heart sounds are heard easier when the transmission is good, and the transmission

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15 Wiggers, C. J. *Modern Aspects on the Circulation in Health and Disease*, Philadelphia, Lea & Febiger, 1923.

16 Cossio, P. *Semiologia cardiovascular*, Buenos Aires, El Ateneo, 1935.

is directly associated with the degree of contact between the heart and the thoracic walls

Volume curves have demonstrated that the volume of the heart at the end of the systole of a strong contraction is smaller than that at the end of the systole of a weak contraction. This means that at the end of the strong systole the relation between the heart and the thoracic wall is less intimate than at the end of the weak systole. The small degree of contact between the heart and the thoracic walls at the end of the strong systole causes a poor transmission of the acoustic phenomena which are produced in this moment, namely, the second heart sound. This explains why though the second sound of the strong contraction is originally stronger than that of the weak contraction, it is heard as if it were less intense.

To summarize, discordant alternation of the second sound, such as that observed in three of the four cases in which alternation was present, is produced because the second sound of the weak contraction is more apparent than the second sound of the strong contraction when listened to at the precordium. This is due to contact between the heart and the thoracic wall at the end of the systole of the weak and the strong contraction.

This explanation of discordant alternation of the second sound noted by us in three of four patients with alternation of the pulse beats makes it easy to understand the mechanism of concordant alternation in the other patient, whose record showed agreement between the height of the pulse beat and the intensity of the second sound. The conspicuous enlargement of the heart of this patient assured a perfect contact between the heart and the thoracic wall, notwithstanding the changes in the volume of the heart at the end of strong and weak contractions, that is, the transmission of the sounds from their original site to the region of precordium where they were audible was equally good in both contractions, therefore the increase of intensity of the second sound of the strong contraction over the second sound of the weak contraction.

The relation between alternation of the first sound and alternation of electrocardiographic complexes that was present in two cases followed strictly the relation between the complexes and the alternation of the pulse beats (Poumailloux,<sup>17</sup> Padilla and Cossio<sup>18</sup>). Alternation of the first sound was concordant with alternation of the T wave and discordant with alternation of the QRS complex just as the pulse wave was concordant with alternation of the T wave and discordant with alternation of the QRS complex.

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17 Poumailloux, M. *Le pouls alternat*, Paris, Masson & Cie, 1930.

18 Padilla, T, and Cossio, P. *Alternancia electrica ventricular*, *Semana méd* 1 1573 (June 11) 1931.

The alternation of the first sound encountered in seven cases of alternation of pulse beats and the alternation of the second sound verified in four of the seven cases modifies the view held up to the present, namely, that alternation of the heart sound is exceptional. Moreover, it should be known that alternation of the heart sound is a frequent and perhaps constant manifestation of the alternation of the heart beat. The reason this fact has been so easily overlooked is that auscultation has been the only means of recognizing it. The failure to detect the alternation by auscultation is due to the mild degree in which it generally is present rather than to the fault of the method itself.

The acoustic phenomenon which expresses the alternation of the sounds is in no case so conspicuous as to become evident on auscultation. Generally it is within the limits of perceptibility, and if it is not deliberately sought it will be overlooked.

Failure to make a deliberate examination and ignorance of the manner in which the sounds are heard by the ear caused the alternation to be overlooked in case 1, notwithstanding careful auscultation of the heart. The alternation was revealed only when a graphic record was obtained to register the gallop rhythm that was present. After the alternation of the first sound was discovered in the graphic record it was detected by auscultation.

To eliminate the possibility of the sounds being heard by mere suggestion, the usual proofs and counterproofs were employed, and the presence of the alternation was confirmed.

A deliberate examination for alternation of the heart sounds and the knowledge that it could be heard with the ear made possible its recognition in the other six cases before any graphic record was obtained. Moreover, in two cases in which alternation of the pulse beats had escaped detection by feeling the pulse, it was discovered by listening to the heart sounds. The alternation was later confirmed by graphic records.

The alternation of the sounds is recognized by the ear by small changes in their intensity, pitch and sound from one cycle to the other, i. e., one sound is more intense, higher pitched and dryer than the same sound of the following cycle, and so on.

These sounds the intensity and pitch of which change alternately from one cycle to another may succeed one another regularly, or a certain irregularity may be present. In the later case it seems as if the sounds of the weak heart contraction should be nearer to the preceding, than to the following, cycle, instead of remaining equidistant from both. The slight irregularity which the ear can perceive is independent of cardiac rhythm, which remains regularly. The irregularity is due to

a real anticipation of the second sound in the cardiac cycle in which a weak first sound is produced by the shorter duration of the systole of this beat

#### CONCLUSIONS

In seven cases in which different degrees of pulsus alternans were present the graphic record of the heart sounds showed alternation of the first sound in all cases and alternation of the second sound in only four cases

The alternation of the first sound was concordant in all cases with the alternation of the pulse beats. In one case only it coexisted and was concordant with an alternation of the T wave in the electrocardiogram. In another case it coexisted and was discordant with an alternation of the QRS complex.

Alternation of the second sound was concordant with alternation of pulse beats in one case and discordant in three cases. The discordance between alternation of the second heart sound and the pulse beats is associated with its transmissibility from the site where it originates to the place where it is heard in the precordium.

Deliberate precordial auscultation and a mental image of the way the alternation of sounds is perceived enabled recognition of the alternation in all cases. In two of four cases in which alternation of the first and of the second sound was present, the alternation of the first sound was perceived easier than that of the second sound.

Alternation of the sounds is detected by means of auscultation by the slight differences in the intensity, pitch and sound that the same sound shows in two successive cardiac cycles. In certain cases there may be a slight typical change in cadence, namely, of the rhythm of their succession.

# NEPHROSIS WITH UREMIA FOLLOWING TRANSFUSION WITH INCOMPATIBLE BLOOD

REPORT OF SEVEN CASES WITH THREE DEATHS

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Since recognition and classification of the blood groups have become general, serious posttransfusion reactions have been infrequent. However, the publication of Bordley's<sup>1</sup> report has focused attention on a striking syndrome following transfusion with incompatible blood. He reported three such reactions and, after extensive search of the literature, fourteen adequately described additional instances. Subsequently other observers have published their experiences with this reaction.<sup>2</sup> The clinical and pathologic similarities in all the cases reported are striking. There is sufficient evidence to indicate that the reaction is the result of hemolysis of the donor's incompatible red blood cells. A typical reaction is characterized by an immediate diminution in the output of urine (in instances of severe involvement, by complete suppression) and hemoglobinuria,<sup>3</sup> within a few hours a moderate degree of icterus appears, the nonprotein nitrogen content of the blood rises gradually and within a few days reaches a high level, and a progressive state

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1 Bordley, J. Reactions Following Transfusion of Blood, with Urinary Suppression and Uremia, *Arch Int Med* **47** 288 (Feb) 1931

2 (a) Stetson, R. E. Causes and Prevention of Posttransfusion Reactions, *S Clin North America* **13** 319 (April) 1933. (b) DeGowin, E. L., and Baldridge, C. W. Fatal Anuria Following Blood Transfusions. Inadequacy of Present Tests for Compatibility, *Am J M Sc* **188** 555 (Oct) 1934. (c) Irsigler, F. J. Uramie nach Bluttransfusion, *Zentralbl f Chir* **58** 1682 (July 4) 1931. (d) Polayes, S. H., and Lederer, M. Reactions to Blood Transfusion, *J Lab & Clin Med* **17** 1029, 1932. (e) von Deesten, H. T., and Cosgrove, S. A. Renal Insufficiency Following Transfusion. Recovery After Venesection, *Ann Int Med* **7** 105, 1933. (f) Johnson, R. A., and Conway, J. F. Urinary Suppression and Uremia Following Transfusion of Blood, *Am J Obst & Gynec* **26** 255, 1933

3 There is little doubt that hemolysis of red blood cells is responsible for the reaction, but accurate chemical and spectroscopic studies of the exact hemoglobin breakdown products which appear in the urine have not been mentioned in the available reports as far as we know

of uremia develops. The uremia may end fatally, or the sudden onset of diuresis may be followed by rapid recovery. While it is not uncommon for chills, dyspnea or pain in the lumbar region to occur during the early part of the transfusion, these immediate symptoms may be absent.

In cases studied at necropsy a similar alteration in the kidneys has been seen, affecting various parts of the uriniferous tubule and associated with the precipitation of hemoglobin or its derivatives. Some observers<sup>4</sup> have found the lesion to be identical with that of patients with blackwater fever dying with urinary suppression. In about half the autopsies recorded focal necrosis was noted in the liver.

During the past six years about two thousand transfusions have been performed in the third medical and surgical divisions of Bellevue Hospital, during which time six reactions of incompatibility have occurred, making an incidence of approximately 0.3 per cent.

The seriousness of these reactions and the recent revival of interest in them have prompted us to report our experience in this regard.

#### REPORT OF CASES

**CASE 1**—F. B., a white man aged 55, was admitted to Bellevue Hospital on July 31, 1930, with diffuse inflammation of the right foot. He was known to have had diabetes mellitus for years. The infection of the foot persisted and was complicated by gangrene of two toes and osteomyelitis. On August 16 the right foot was amputated, but the stump did not heal satisfactorily. On Jan. 2, 1931, the patient's temperature suddenly rose to 105° F. The blood pressure was 110 systolic and 60 diastolic. The urine was normal.

On January 5 the patient's blood was typed and found to belong in group 1 (Jansky). The donor's blood was not typed, but cross-matching indicated that there was no agglutination of the red blood cells with the patient's serum. On this day the patient was given 500 cc. of blood by the direct method. Fifteen minutes later he vomited and had a severe chill. Urinalysis on the same day showed protein 1+, a few red blood cells and a 4+ benzidine reaction. The next morning jaundice was noted. The output of urine was diminished to less than 5 ounces (150 cc.) for twenty-four hours. On the fourth day the nonprotein nitrogen content reached 150 mg. per hundred cubic centimeters of blood, and the output of urine was 10 cc. for twenty-four hours. On the sixth day the patient passed 3 cc. of urine. The nonprotein nitrogen content was 102 mg. per hundred cubic centimeters of blood. The patient died in coma on the seventh day following the transfusion. The donor's blood group was not determined, and cross-matching was not repeated after the transfusion.

*Gross Postmortem Examination*—The body was that of a well developed and well nourished white man of about 50. The amputation stump of the right foot (at the metatarsophalangeal joint) showed slight suppuration of the edges. There were several irregular areas of ecchymosis from 1 to 3 cm. in diameter in the

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<sup>4</sup> Wakeman, A. M., Morrell, C. H., Eisenman, A. J., Sprunt, D. L., and Peters, J. P. The Metabolism and Treatment of Blackwater Fever, *Am. J. Trop. Med.* **12**: 407 (Nov.) 1932. Dudgeon, L. Blackwater Fever, *J. Hyg.* **19**: 208 (Oct.) 1920.

skin of the right leg Limitation of the incision to the abdomen made examination of the thorax difficult The serous sacs were free from fluid or adhesions The heart and lungs were not removed, but small pieces of the lungs were taken for microscopic examination

The spleen was enlarged, and its capsule was tense and smooth It weighed 500 Gm There were numerous punctate hemorrhages in the capsule On section its pulp was soft and dark red, and it oozed blood The follicles could not be seen

The liver was enlarged, weighing 2,450 Gm Its capsule was smooth, thin and glistening On section there were prominent lobular markings Focal areas were a light tawny yellow suggestive of fatty change The surface was fairly firm The gallbladder, bile ducts and portal vein were normal

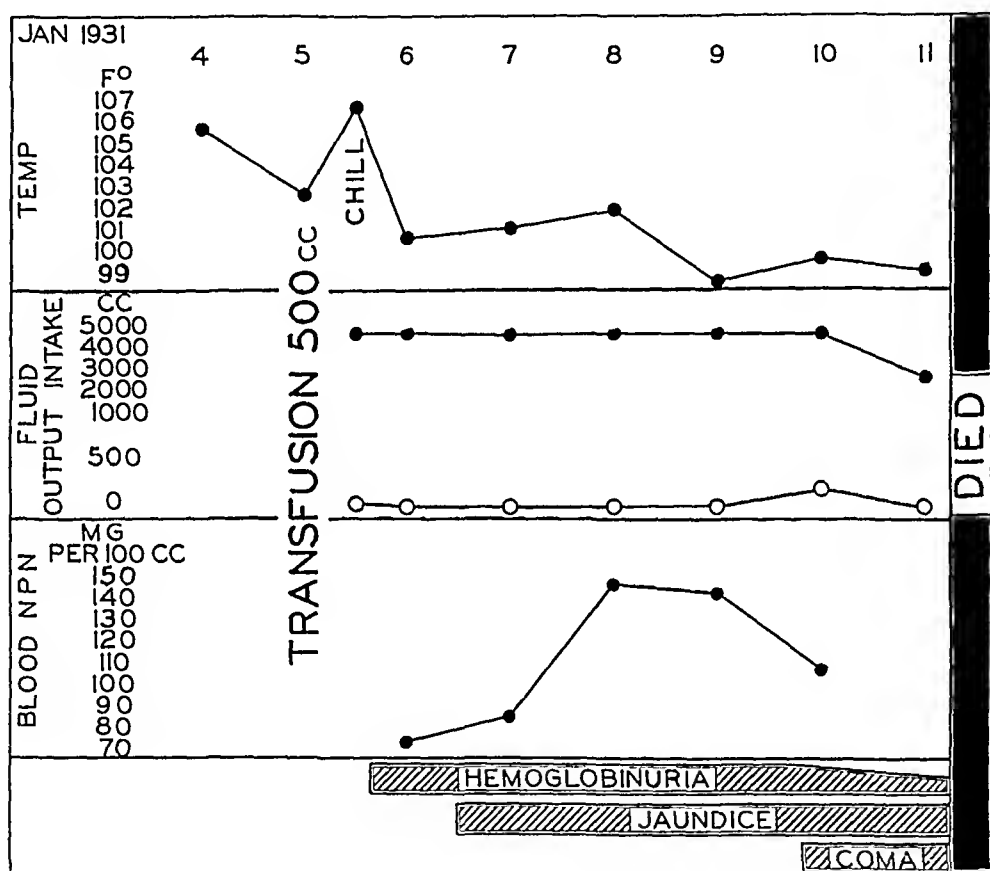


Fig 1 (case 1) —F B, a white man aged 55, had cellulitis of the foot The patient's blood belonged in group 1 (Jansky) The donor's blood group was not determined, but cross-agglutination of the red blood cells with the patient's serum was negative before the transfusion No recheck was made after the transfusion

The pancreas and adrenal glands showed no visible changes The appearance of the stomach and intestines was not remarkable

The kidneys were enlarged, each weighing 235 Gm The capsules stripped easily, leaving a fairly smooth, milk-gray surface On section there was thought to be marked hyperemia of the medullary pyramids The corticomedullary junction was sharply demarcated The pelves, ureters and bladder showed no changes The testes were normal in size and appearance



*Microscopic Postmortem Examination*—Sections of the lungs showed no inflammatory changes. Marked hyperemia and occasional areas of collapse were noted. There was moderate anthracotic pigmentation.

**Liver** Sections from different areas of the liver showed similar lesions. There were scattered areas of necrosis in the lobules, tending to be central in location, sometimes involving the inner third of each lobule. In some of these areas there was hemorrhage. The adjacent hepatic cords were deeply pigmented by golden yellow and golden brown, highly refractive pigment. Kupffer's cells were filled and enlarged with deep black-brown pigment. There was a marked proliferation of fixed tissue cells in the periportal areas. Small numbers of plasma cells and leukocytes were present. There was no increase in the amount of connective tissue in these areas.

**Spleen** There was marked hyperemia of the sinuses, with considerable hemosiderosis, both intracellular and extracellular. The splenic follicles were small, and the so-called germinal centers were not clearly visible. There was moderate arteriosclerosis.

**Pancreas** Sections from the head of the pancreas showed no noteworthy changes.

**Kidneys** Many blocks were taken from both kidneys, and they revealed a widely distributed alteration. Sections were stained with hematoxylin and eosin, the Van Gieson and the Weigert elastic tissue stain, the Gram-Weigert stain, and Mallory's phosphotungstic acid-hematoxylin stain. Sections were stained for reticulum by the method of Foot and Foot, for iron by the Perl method and the Turnbull method, for hemoglobin by the Lepehne method and the Brown method and for fat with sudan IV.

The glomeruli were not reduced in number and were intact except for focal thickening of the basement membrane and of the walls of the afferent arterioles. The loops were patent, as a rule, and contained erythrocytes. In some sections Bowman's capsule appeared distended, and there was an increase in the intracapsular space. However, many glomerular capsular spaces did not appear distended, and the capsule invested the contained tufts closely.

The medium-sized vessels showed no changes. The inner elastic layer was intact.

The interstitial stroma appeared edematous, with the tubules separated from each other by various intervals. This was most marked at the corticomedullary junction. In all sections there were focal areas exhibiting proliferation of histiocytes, plasma cells and a few polymorphonuclear leukocytes in the interstitial stroma as well.

Under low magnification what appeared at macroscopic examination to be medullary hyperemia was seen to be due to the presence of large reddish brown crystal masses precipitated in the collecting tubules and dilating their walls.

The tubules showed a severe regressive change. Their lumens appeared large, owing to desquamation or shrinkage of the lining cells or to distal obstruction.

Eosinophilic debris was seen to be free in the lumens of the proximal tubules. Farther down the tubule the cast formation encountered was remarkable. In the thin and thick portions of Henle's loop and the distal convoluted segment deeply eosinophilic droplets formed masses and casts. At first glance they appeared to be red blood cells, but comparison with the erythrocytes within the vessels near-by revealed that they were as a rule either much smaller or much larger, rarely the same size.

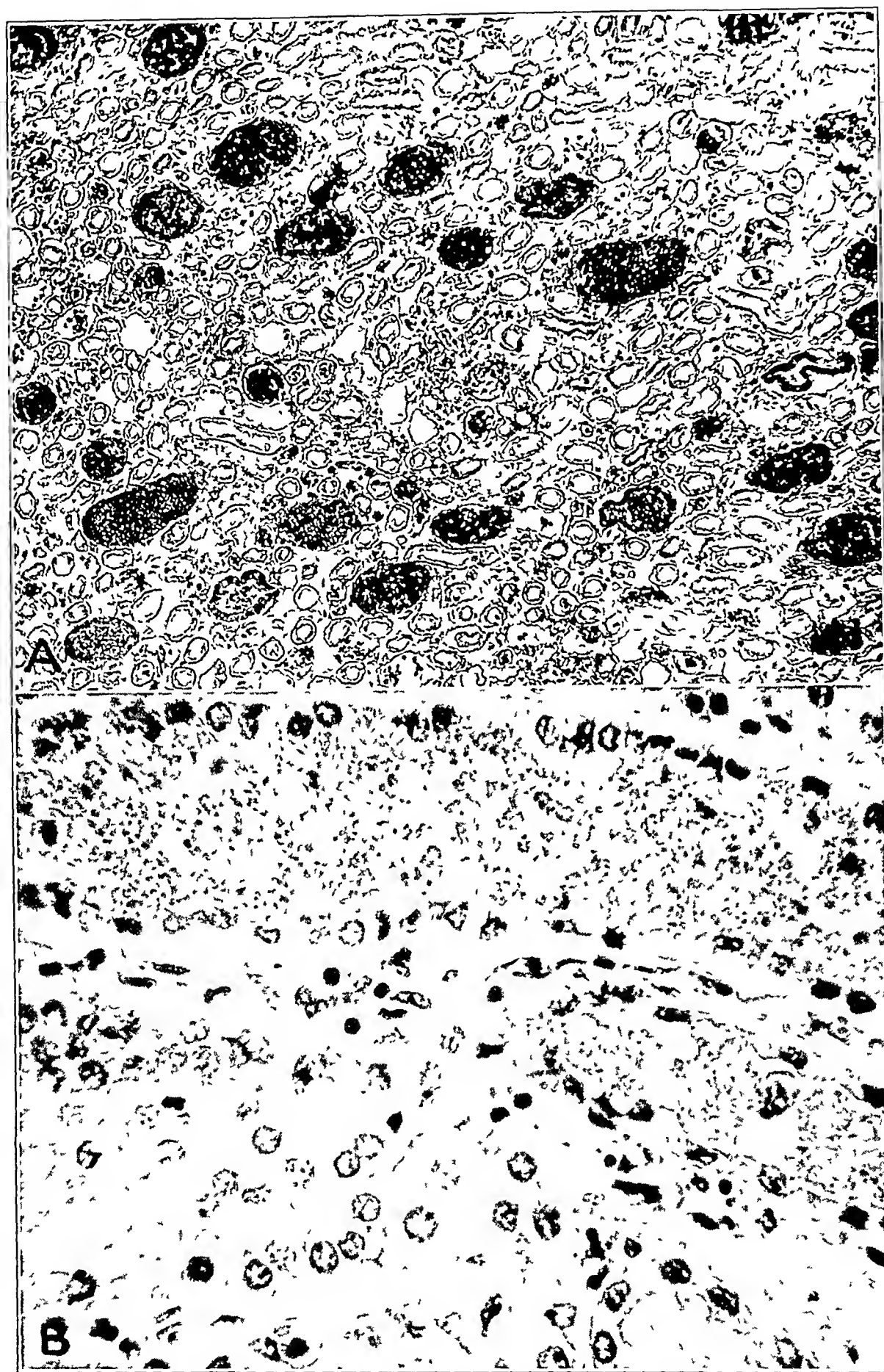


Fig 2 (case 1) —*A*, a low power view of a section through the medulla of the kidney. Note the formation of large obstructing pigment masses of hematin crystals and granules. *B*, a high power photomicrograph showing in more detail the tubular degeneration, interstitial edema and peculiar granular casts.

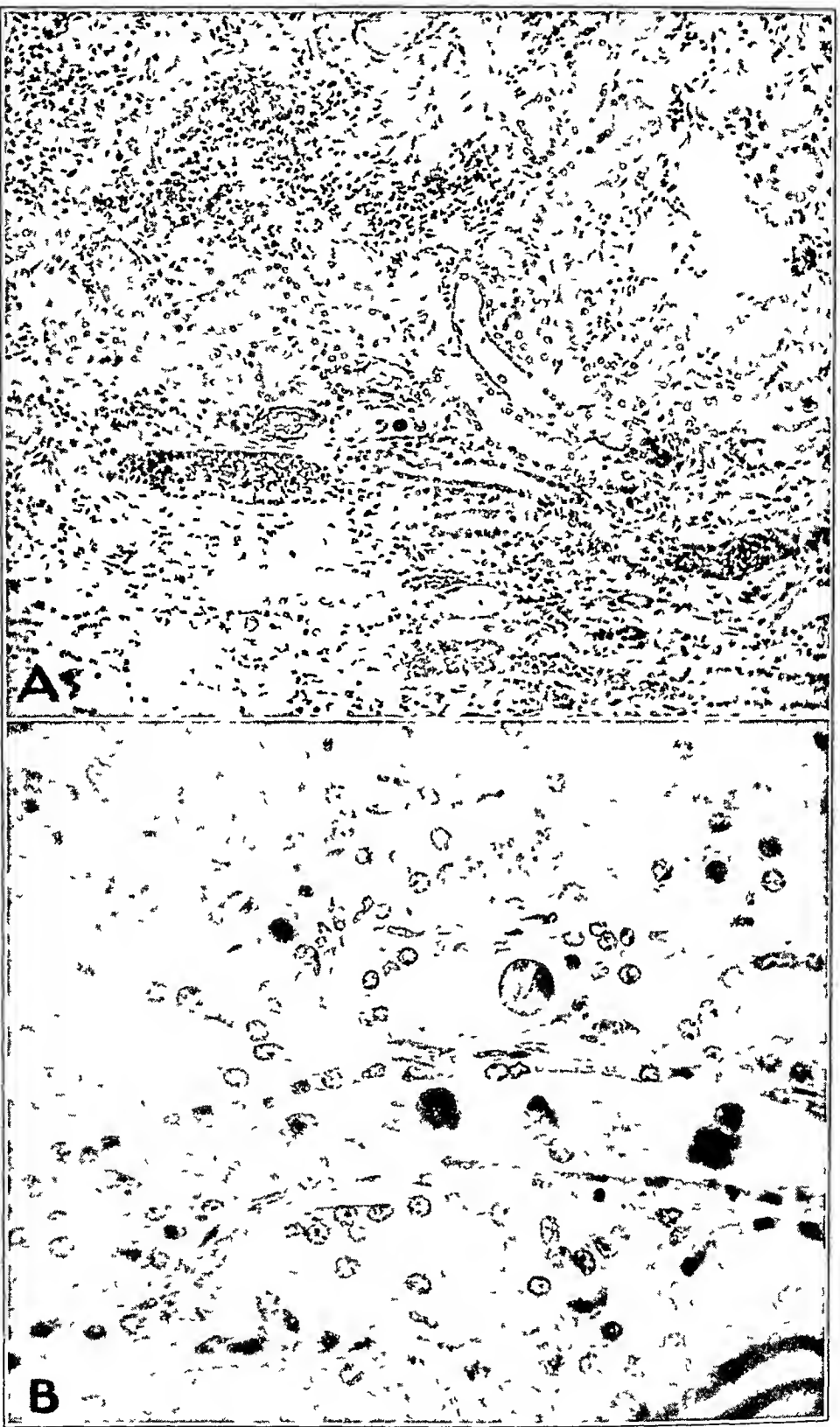


Fig 3 (case 1) —*A*, a low power photomicrograph of a section through the cortex including a number of Henle loops, illustrating the interstitial edema, proliferation of fixed tissue cells, tubular dilatation and epithelial degeneration. The granular casts were abundant in segments of the Henle loops and the distal convoluted tubules. *B*, a high power photomicrograph of a section of the kidney, illustrating calcification in the Henle loops and a solitary milium calculus in one tubule.

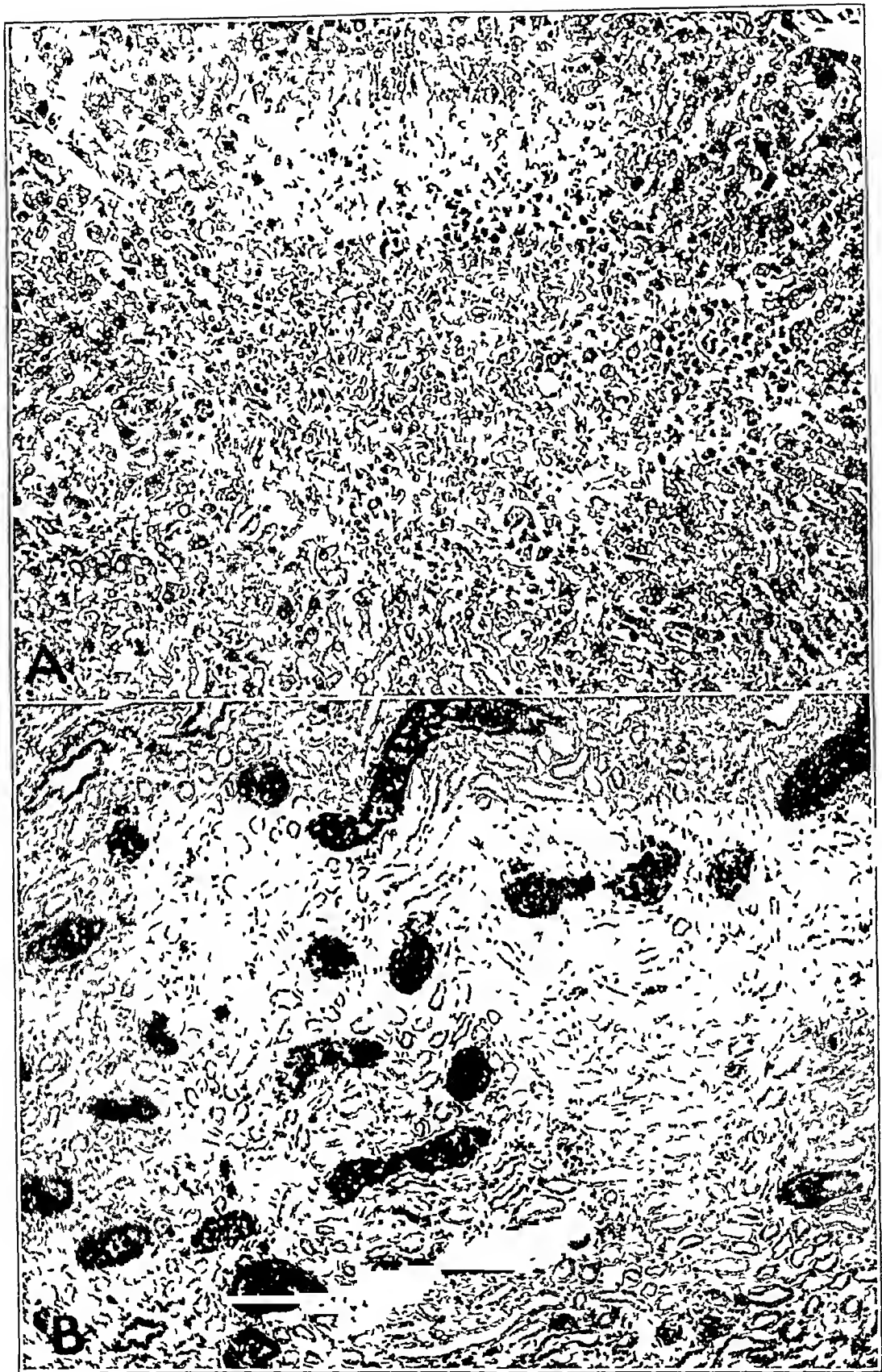


Fig 4—*A*, a low power photomicrograph of a section of the liver (case 1) illustrating the central focal necrosis *B*, a low power photomicrograph illustrating the hematin granular masses obstructing the collecting tubules (case 4)

In some instances these droplets were coccoid. Sometimes they were discrete, and elsewhere they were seen embedded in a faintly eosinophilic matrix. This was best seen in sections stained with Mallory's phosphotungstic acid-hematoxylin stain.

Hemosiderin granules were seen in small numbers in the epithelium of the distal convoluted segments. The intact epithelium of the proximal and distal tubules showed various regressive changes, including loss of the outline of the cells, marked vacuolation of the cytoplasm and rarely a loss of nuclei. No intracytoplasmic eosinophilic granules were seen.

The most severe lesions were seen in the Henle loops. Almost all these loops contained granular casts composed of deeply eosinophilic particles or globules. In addition, in some there were casts of desquamated epithelial cells and tiny calcified masses, while others contained (new?) lining epithelial cells which were flattened, with small densely chromatinic nuclei. No mitoses were seen.

In the collecting tubules the casts were larger and brown (also in unstained sections) and were associated with marked dilatation and flattening of the lining cells (due to pressure atrophy). In places the cells were desquamated. The majority of the collecting tubules showed these casts. In some of the lining cells hemosiderin granules were present. Lepelne's stain,<sup>5</sup> which employs benzidine, was applied to paraffin sections, and the suspicion that the casts were composed of hemoglobin droplets was confirmed.

The red blood cells in the renal vascular bed showed no individual changes.

Stains for iron (the Perl and the Turnbull method) revealed that the casts contained no free iron. The only demonstrable pigment containing free iron was seen in the form of the hemosiderin granules previously noted.

*Diagnosis*—The pathologic diagnosis was acute nephrosis, mild arteriolar nephrosclerosis, focal necrosis and hemorrhage of the liver, septic softening of the spleen and infection of the amputation stump of the right foot.

**CASE 2**—A K, a Puerto Rican housewife aged 25, was admitted to the hospital complaining of vaginal bleeding for three days after attempted abortion. The past history was irrelevant.

The patient had marked secondary anemia. The blood pressure was 100 systolic and 70 diastolic. Urinalysis was not performed. The patient's blood belonged in group 1 (Jansky).

On July 9, 1932, a transfusion of 500 cc of group 1 blood was given by the direct method, with no reaction. The next day 360 cc of group 1 blood from another donor was given, with no unusual reaction. On August 6, a transfusion of 500 cc of blood from a third donor, the patient's husband, was given. This donor's blood belonged in group 1 (Jansky). An hour and a half after the transfusion the patient vomited and had a chill lasting for twenty-five minutes. Six hours later she complained of pain in the lower part of the back and difficulty in breathing. The pulse rate was 134, and the temperature was 105 F. Urinalysis at this time showed many red blood cells and protein 4+. The nonprotein nitrogen content of the blood was 75 mg per hundred cubic centimeters. On August 8 jaundice was noticed for the first time, and vomiting began. The output of urine was 2 ounces (60 cc) for this twenty-four hour period. On August 10 the nonprotein nitrogen content of the blood was 100 mg per hundred cubic centimeters. Jaundice and vomiting persisted, and edema appeared on the face and over the sacral region. On August 17 the nonprotein nitrogen content of the

<sup>5</sup> Lepelne, G. Zerfall der roten Blutkörperchen beim Ikterus infestiosus (Weil). Ein weiterer Beitrag zur Frage des hematogenen Ikterus, des Hämoglobin- und Eisenstoffwechsels, Beitr z path Anat u z allg Path **65** 163, 1919.

blood reached 180 mg per hundred cubic centimeters. On August 20 the output of urine suddenly increased, and the patient recovered rapidly, being discharged on September 27. After the transfusion the regrouping of the bloods of the patient and donor by Dr R Stetson confirmed their identity as belonging to group 1 (Jansky).<sup>6</sup> The patient was reexamined on March 19, 1933. Urinalysis revealed no abnormality. The nonprotein nitrogen content of the blood was 38 mg per hundred cubic centimeters.

CASE 3—J C, a white man aged 42, was admitted to the hospital on July 22, 1930, because of a crushing injury of the left foot. His past history was unimportant. The blood pressure was 134 systolic and 85 diastolic. Urinalysis showed a specific gravity of 1.020, no protein, no sugar and a normal microscopic appearance. The blood belonged in group 1 (Jansky). The patient received 500 cc of

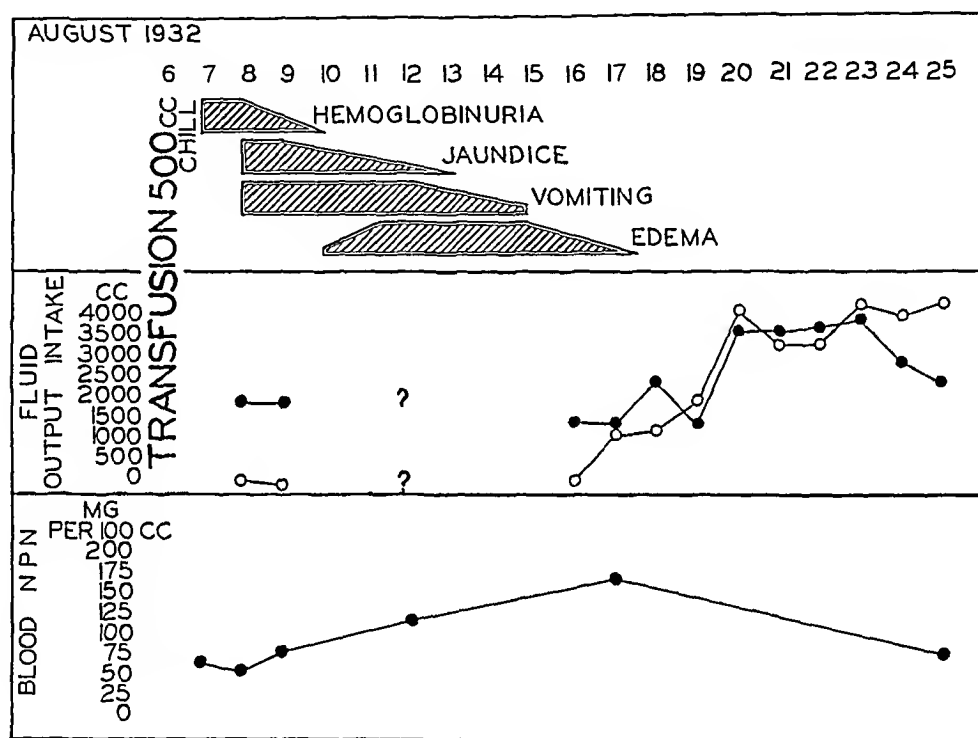


Fig 5 (case 2)—A K, a white woman aged 25, had a uterine hemorrhage and anemia. Her blood and the bloods of the three donors belonged in group 1 (Jansky). The results of cross-agglutination tests before the third transfusion were negative whereas following this transfusion there was difference of opinion (for a full discussion of this case see the article by Stetson<sup>2a</sup>). A reaction occurred after the third transfusion.

group 1 blood by the direct method on July 23 and also on July 25 from two different donors, with no reaction. On July 28 he received 500 cc of blood from a third donor. During the transfusion the patient complained of weakness. Immediately after the transfusion he became cyanotic, perspired profusely and complained of being cold. An urticarial rash appeared on the arms and back. A chill developed which lasted for twenty-five minutes. One half hour after the transfusion the temperature was 105 F. The donor's blood was retyped and found to belong in group 2.

<sup>6</sup> Full discussion of this case was published in a paper by Dr Stetson<sup>2a</sup>.

Two hours after the transfusion the patient passed frankly red urine, containing no red blood cells. The benzidine reaction was strongly positive. The nonprotein nitrogen content of the blood was 70 mg per hundred cubic centimeters. Vomiting began that evening. The next morning jaundice appeared. The urinalysis showed protein 4+, numerous red blood cells, white blood cells and hyaline and granular casts. The output of urine was greatly diminished. The patient's condition became progressively worse. On August 11, two weeks after the transfusion, the nonprotein nitrogen content of the blood reached 520 mg per hundred cubic centimeters. The patient was stuporous and dehydrated, and there were fibrillary twitches of the facial muscles. On August 12 he had several clonic convulsions. There was no edema. On August 16 bilateral nonsuppurative

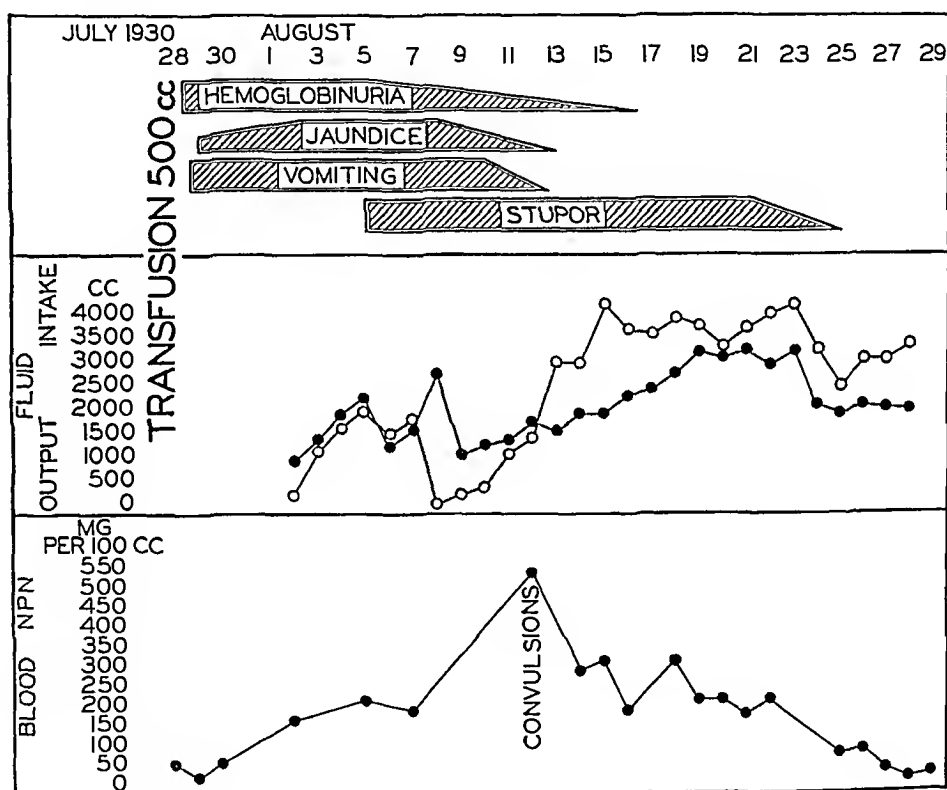


Fig 6 (case 3) —J C, a white man aged 42, had anemia due to loss of blood from an injury to one foot. The patient's blood belonged in group 1 (Jansky), the third donor's blood proved to belong in group 2. A reaction occurred after the third transfusion.

parotitis developed which resolved after six days. On August 13 there was a sudden increase in the output of urine. Afterward the output of urine continued high, and the nonprotein nitrogen content gradually fell. Vomiting ceased, and the patient's mental state returned to normal. He was discharged improved on September 19. The nonprotein nitrogen content of the blood had returned to normal, but urinalysis still showed a trace of protein, many red blood cells and many hyaline casts. Impairment of the maximum concentrating power was persistently marked. Reexamination on Feb 2, 1932, showed that the concentrating power was normal. Urinalysis was normal.



CASE 4—T C, a Puerto Rican housewife aged 24, was delivered of a normal child at term on Dec 30, 1930. Evidence of postpartum pelvic inflammation developed. There were repeated chills, and the temperature rose to 104 F. On Jan 3, 1931, urinalysis was normal. The blood belonged in group 1 (Jansky). A group 1 donor was selected. On direct matching there was no agglutination of the donor's red blood cells after twenty minutes. On January 5 the patient was given 400 cc of blood by the direct method. A few hours later frankly red urine which contained hemoglobin was passed. The next morning jaundice was noted. The output of urine was less than 3 ounces (90 cc) a day for the rest of the course. On January 8 the nonprotein nitrogen content of the blood was 110 mg per hundred cubic centimeters. Edema did not develop. The patient became

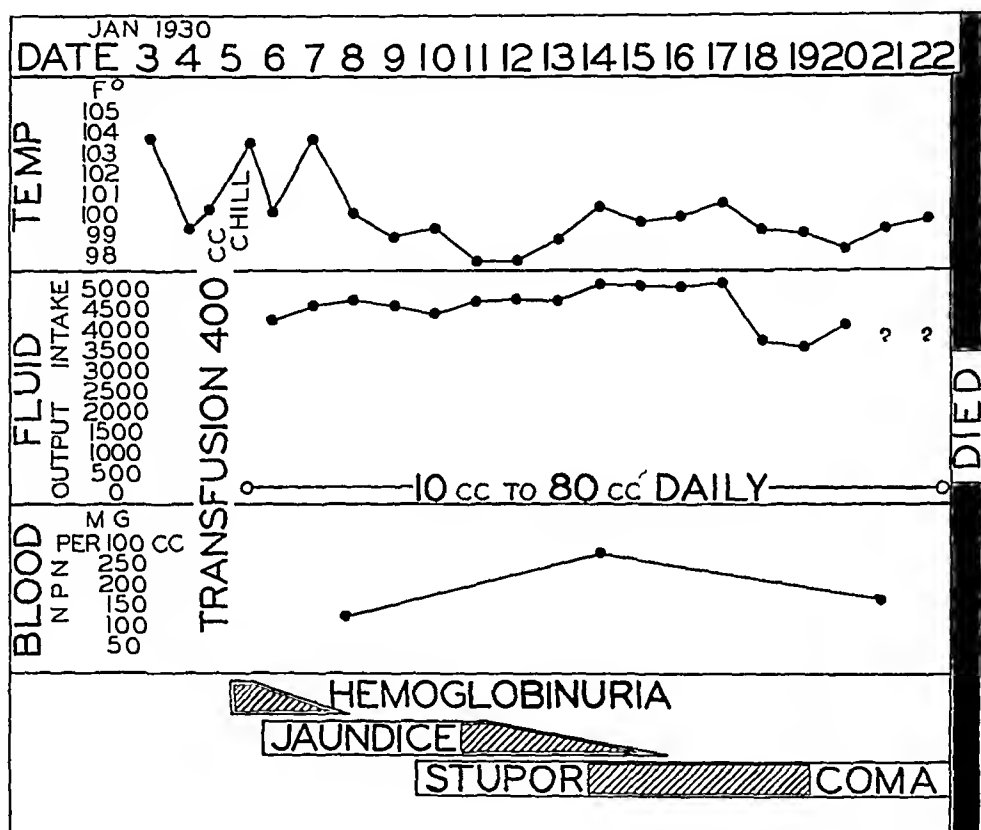


Fig 7 (case 4)—T C, a white woman, aged 24, had postpartum sepsis. Her blood belonged in group 1 (Jansky). The donor's blood proved to belong in group 2. Cross-agglutination before the transfusion was reported as negative.

stuporous and dehydrated. The nonprotein nitrogen content of the blood rose to 245 mg per hundred cubic centimeters and subsequently fell to 180 mg. Urinalysis showed protein 4+ and innumerable red blood cells. A pelvic abscess developed on January 21 which required incision and drainage. The patient remained stuporous and died on January 24. Retyping of the donor's blood showed it to belong in group 2.

*Gross Postmortem Examination*—The body was that of a well developed white woman in a fair state of nutrition. There was moderate generalized subcutaneous edema. There was an operative incision about 10 cm long in the right



lower quadrant of the abdomen held together by several deep sutures. A long rubber dam drain protruded through the incision, and on it was a small amount of thin yellow purulent fluid.

The peritoneum was everywhere dull and covered with a creamy purulent exudate. There was a large amount of light greenish yellow fluid free in the cavity. The small intestines were loosely matted together and considerably distended. Flakes of fibrin could be brushed off the serous surfaces of the intestines.

The pleural and pericardial sacs were free from fluid or adhesions.

The lungs were crepitant throughout. Considerable edema and hyperemia were noted in the lower lobes in their dependent portions. No areas of consolidation could be made out. The bronchi contained frothy fluid.

The heart was not enlarged, weighing 250 Gm. There were no visible changes in the endocardium, valves, myocardium or epicardium. The coronary vessels were normal. The aorta was normal throughout its length.

There were no visible changes in the gastro-intestinal tract, except for the fibrinous exudate on the serous surface.

The liver was slightly enlarged, weighing 1,550 Gm. The capsule was not thickened and was altered only by the fibrinous exudate on the surface. On section the lobular markings were not accentuated. The surface was grayish brown.

The gallbladder, bile ducts and portal vein were normal.

The pancreas and the adrenal glands were normal.

The spleen was slightly enlarged and weighed 270 Gm. Its capsule was smooth. On section the organ was soft and purplish red, and the follicles could not be made out. The splenic artery and vein were patent.

Both kidneys were enlarged and were embedded in a moderate amount of fat. On section, the capsule came away easily, leaving a smooth, moist surface which was mottled grayish red. The cortex was slightly swollen and pale gray, while the medulla appeared hyperemic. In the medullary region of the right kidney grayish white streaks extending into the tips of the papillae were distinctly seen. In places these streaks could be seen in the cortex. The whole cut surface of the right kidney presented a swollen, ill defined appearance. The pelvis of the right kidney was markedly hyperemic and contained purulent urine.

On section of the left kidney the cortical-medullary junction was sharp. The medullary pyramids appeared markedly hyperemic. The pelvis and ureter were free from inflammatory changes and contained no pus. The bladder when opened was seen to be contracted, the lining was diffusely hyperemic and in places was covered with a gray, necrotic membrane.

The uterus was slightly enlarged and somewhat boggy in consistency, although the myometrium was of normal thickness. The right tube and ovary were enlarged, matted together, covered with a purulent exudate and plastered on the fundus of the uterus. On section the right ovary was about three times the normal size, and was the seat of multiloculate abscesses. The fallopian tube on this side also was thickened and adherent to the ovary. Its lumen contained the same type of thick greenish yellow pus. The right broad ligament was the seat of a large abscess containing greenish yellow pus. This extended into the pouch of Douglas, which was filled with pus. The endometrium was hypertrophied and on one side presented an area of marked edema. The cervix was soft, the os admitting one finger. The vagina showed nothing unusual.

The head was not examined.

*Microscopic Postmortem Examination*—Sections of the myocardium revealed no significant changes. There was moderate fiber and nuclear hypertrophy.

*Lungs* There were patchy areas of collapse and areas of pulmonary edema. In one section there were areas of hemorrhage and a fine network of fibrin in the alveolar spaces. There were no inflammatory changes in the bronchi.

*Spleen* The malpighian bodies were of normal size. So-called germinal centers were not present. There was moderate arteriosclerosis. The venous sinuses were prominent and gorged with blood. Pulp cells were prominent.

*Liver* There were focal areas of fatty change and some loss of staining power. No hemorrhages were seen. Kupffer cells were not particularly prominent. The bile ducts showed no changes.

*Kidneys* Section of the right kidney was complicated by the presence of a marked, diffuse suppurative process with particular involvement of the medulla. In this section, however, there were, in addition, blood casts of various types. Sections of the left kidney showed none of the suppurative process seen in the right kidney. A widespread degenerative tubular lesion and moderate edema of the interstitial stroma were noted.

Under low magnification the collecting tubules could be seen to be overdistended and plugged with large brown casts. These were likewise brown in unstained sections. In places the tubules were free from such casts, but even in these tubules the lining epithelium was desquamated in places or exhibited various regressive changes, consisting of a loss of the outline of the cells and nuclei and some granular degeneration. There was marked vacuole formation in the intact tubules. The glomeruli were normal in size and number. They exhibited no individual changes of any note. The blood vessels and arterioles particularly were well preserved.

Elsewhere the uriniferous tubules, particularly in Henle's loop and the distal convoluted segment, showed various stages of a degenerative process. In some the lining epithelium was completely desquamated, in others, it was replaced by flattened epithelium and pyknotic nuclei. In others the epithelium merely showed a loss of nuclei. In all these units there was marked formation of casts composed of deeply eosinophilic masses. In places these masses were discrete, elsewhere they were embedded in an albuminous mass. The droplets varied in size from coccoid granules 1 or 2 microns in diameter to droplets larger than a red blood cell. Deeper in the uriniferous tubule the casts changed from deep red to reddish brown in the collecting tubules. In unstained sections these casts and the convoluted tubules had a faint reddish brown tinge, whereas in the collecting tubules they were definitely brownish. Stains for iron revealed practically no free iron in these casts or in the epithelium lining the tubules. Lepehne's<sup>5</sup> stain confirmed the impression that the casts contained hemoglobin.

*Uterus and Ovary* Section of the wall of the uterus and ovary showed a diffuse suppurative exudate on the surfaces, with moderate, fixed tissue proliferation and granulation tissue at the base of the exudate.

*Diagnosis*—The pathologic diagnosis was acute nephrosis, abscess of the right ovary and tube, generalized peritonitis, focal fatty changes of the liver, ascending acute suppurative pyelonephritis on the right side, anasarca, congestion and hyperplasia of the pulp of the spleen, focal collapse of the lungs, emphysema and pulmonary edema.

CASE 5—A H, a white woman aged 25, was delivered of a normal full term infant on Dec 29, 1933. One hour after delivery she complained of a severe, sharp pain in the left side of the chest and presented the picture of shock. A diagnosis of pulmonary embolism was made. Blood transfusion was suggested, and since the patient appeared moribund, time was not taken to determine the blood group of the donor, the patient's husband. Direct matching of the bloods showed no gross agglutination. After 220 cc of blood had been transfused by the direct method the patient suddenly became dyspneic and roused sufficiently to complain of choking. The transfusion was stopped. On the following day the patient passed 9 ounces (300 cc) of frankly red urine, containing hemoglobin.

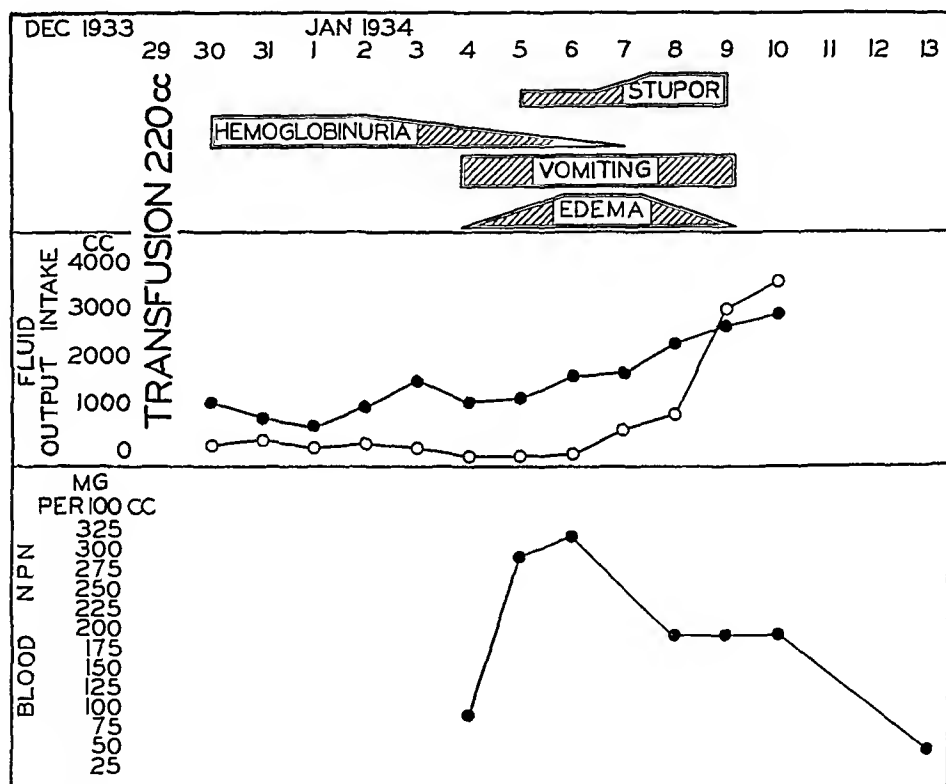


Fig 8 (case 5)—A H, a white woman aged 25, had postpartum pulmonary embolism with shock. The patient's blood belonged in group 1 (Jansky). The donor's blood proved to belong in group 2. There was no cross-agglutination before the transfusion was given.

The oliguria and hemoglobinuria persisted for the next seven days. During this period the patient was in a semistuporous state and vomited continually. The non-protein nitrogen content of the blood had risen to 315 mg per hundred cubic centimeters and the creatinine content to 88 mg. Generalized edema appeared on the sixth day following the transfusion and disappeared on the eleventh day. There was no jaundice. On the eleventh day following the transfusion diuresis set in suddenly. Thereafter recovery was continuous and rapid. The patient was discharged on Jan 13, 1934. Retyping at that time showed that the patient's blood belonged to group 1 (Jansky) and that of the donor to group 2.

CASE 6—M G, a white woman aged 24, entered the hospital on Feb 14, 1929, complaining of profuse vaginal bleeding for three weeks. The temperature was normal. Urinalysis showed no protein, sugar or formed elements. The Wassermann reaction of the blood was negative. The red blood cell count was 3,970,000 and the hemoglobin value 65 per cent. The blood belonged to group 1 (Jansky). On February 21 the patient was given a transfusion, her husband acting as donor. His blood belonged in group 1 (Jansky), and cross-matching of the red cells with the patient's serum showed no agglutination. The direct method of transfusion was used. After 110 cc of blood had been given the patient suddenly became dyspneic and complained of "choking." The transfusion was halted for a few minutes, and the symptoms subsided. The transfusion was then resumed until a total of 400 cc of blood had been given, when the patient again complained of choking and became dyspneic. The transfusion was stopped. A few hours later the patient vomited but had no other complaint. The next morning vomiting reappeared, and distinct jaundice was noticed. On this day (February 28) the patient passed no urine. The nonprotein nitrogen content of the blood was 150 mg per hundred cubic centimeters. The following day she voided  $\frac{1}{2}$  ounce (15 cc) of dark brown urine containing hemoglobin, many red blood cells and protein. For the following ten days the output of urine was  $6\frac{1}{2}$ , 8, 8, 8, 8, 9,  $12\frac{1}{2}$ , 10, ? and 3 ounces (200, 240, 240, 240, 240, 270, 475, 300, ? and 90 cc), respectively. Protein, red blood cells and casts persisted throughout. Hemoglobin was present in all but the last sample of urine collected. Vomiting persisted throughout. The patient passed into a stuporous state, and although no further chemical studies of the blood were made, bedside notes described her as presenting the symptoms of a typical uremic state. She died on March 7, the fourteenth day after the transfusion. There was no rechecking of the blood groups or cross-matching. Permission for necropsy was not obtained.

CASE 7—E H, a Puerto Rican housewife aged 24, entered the hospital on May 1, 1935, complaining of pain in the lower part of the abdomen and vaginal bleeding of one week's duration. A diagnosis of bilateral salpingitis and possible ectopic pregnancy was made. The blood pressure was 86 systolic and 56 diastolic. The urine showed albumin, a few clumped white blood cells, a specific gravity of 1.015, 3,300,000 erythrocytes and 55 per cent hemoglobin. The patient was given palliative treatment, and on May 12 left the hospital at her own request.

Three days later the patient returned to the hospital, complaining of pain in the lower portion of the abdomen and vaginal bleeding. The blood pressure was 94 systolic and 60 diastolic. The urine again showed albumin, a few clumped white blood cells and a specific gravity of 1.020. The left ankle became painful and swollen, a condition diagnosed as gonococcal arthritis. On May 22 the patient was given a transfusion of 500 cc of blood, her husband acting as donor. The bloods of the patient and donor belonged in group 1 (Jansky). During the transfusion the patient stated that she felt "funny," but she was not short of breath and she had no choking sensation or pain in the back. A severe chill developed, which was followed by a rise in temperature to 106 F. Dark urine was passed a few hours later. The following day jaundice was noticed. The output of urine diminished to 15 cc on the second day and to 8 cc on the third day. The non-protein nitrogen content of the blood rose to 60 mg per hundred cubic centimeters on the fifth day and reached 150 mg on the eighteenth day. For the first ten days the patient vomited everything taken by mouth. The specific gravity of the urine remained fixed at a level of from 1.008 to 1.012. Infusions and clyses of a 5 per cent solution of dextrose in saline solution were given daily. The output

of urine reached 900 cc on the seventh day On June 1 the patient became generally edematous, and the parenteral administration of fluid was discontinued The edema disappeared in three days Gradual and uneventful recovery followed the onset of diuresis The bloods of the patient and donor were retyped and were shown to belong in group 1 (Jansky) There was no agglutination of the donor's red blood cells by the patient's serum or of the patient's red blood cells by the donor's serum

On June 13 a test of the renal function showed fixation of the specific gravity and a 10 per cent excretion of phenolsulfonphthalein in two hours as evidence of the severe impairment of the renal function

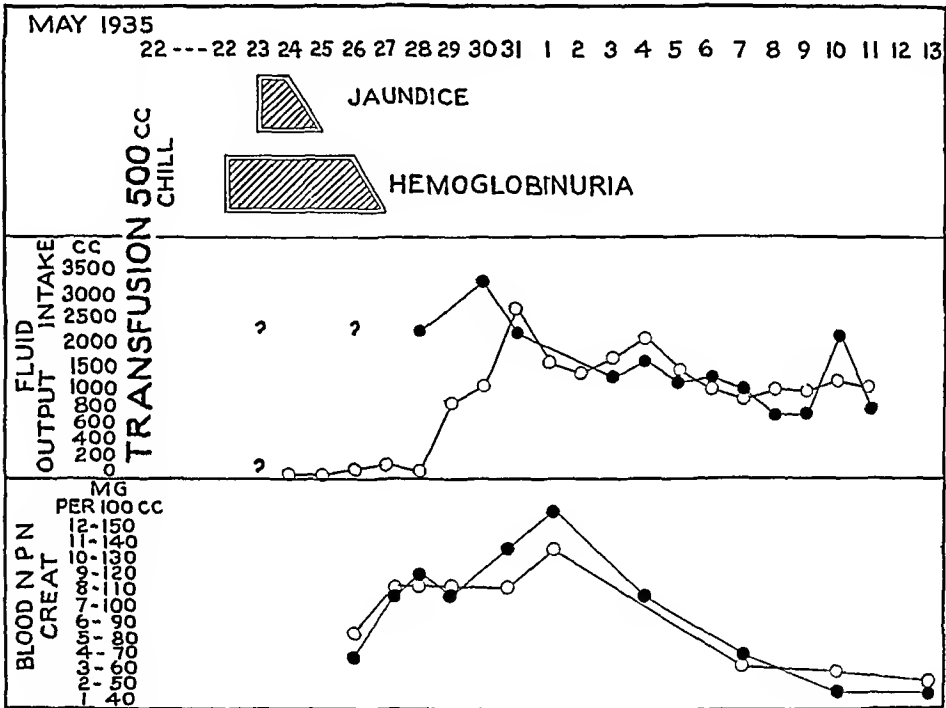


Fig 9 (case 7) —E H, a white woman aged 24, had uterine bleeding and anemia Her blood belonged in group 1 (Jansky), as did also the donor's A recheck of the blood groups and cross-agglutination after the transfusion confirmed these findings

COMMENT

The accompanying table gives a summary of the clinical observations in this series The bloods of all the recipients belonged in group 1 (Jansky) In three instances the reaction followed a transfusion of group 2 blood, in two cases the failure to recheck the blood groups after the transfusion was given left doubt as to the classification, in two cases retyping after the transfusion confirmed the fact that the blood of both the donor and the recipient belonged to group 1 (Jansky)

Alarming symptoms appeared during the transfusion in two cases, no subjective symptoms appeared in three cases and in the remaining two cases the subjective symptoms were vague and were not considered of sufficient importance to warrant the discontinuance of the transfusion

# Summary of the Clinical Data

Patient	Sex	Age	Diagnosis	Blood Group (Jansky)			Transfusion of Blood, Cc *	Reaction During Transfusion	Chmax Reached, Day	Result	Comment
				Recipient	Donor						
F B	M	55	Cellulitis of foot	1	?		500	None	7	Died	One transfusion, vomiting 15 minutes later, donor's blood group not determined, cross matching not repeated after transfusion, necropsy
A K	F	25	Uterine hemorrhage, anemia	1	1		500	None	14	Recovered	Three transfusions with different donors 1½ hours after third transfusion vomiting, chill, dyspnea and pain in lumbar regions rechecked after transfusion confirmed blood grouping †
J O	M	42	Crushing injury to foot with hemorrhage, anemia	1	2		500	Weakness	16	Recovered	Three transfusions with different donors, immediately after third transfusion, chill lasting for 25 minutes, cyanosis and diffuse urticarial rash, one half hour later, temperature of 105° F
T O	F	25	Postpartum sepsis, pelvic abscess	1	2		400	None	19	Died	One transfusion, death 3 days after drainage of pelvic abscess, necropsy
A H	F	25	Shock following postpartum pulmonary embolization	1	2		200	"Choking" sensation, dyspnea	11	Recovered	One transfusion
M G	F	24	Incomplete abortion, anemia	1	1 ?		400	"Choking" sensation, dyspnea	14	Died	One transfusion, blood groups and cross matching not rechecked after transfusion
T H	F	24	Incomplete abortion, anemia	1	1		500	"Funny" feeling	7	Recovered	One transfusion, recheck of blood groups proved that bloods of donor and recipient belonged in group 1 (Jansky) and that there was no cross agglutination

\* In all instances the direct method was used  
† See Stetson <sup>2a</sup> for detailed discussion of this case

There appeared to be no striking relationship between the amount of blood transfused and the severity of the reaction. Two patients who received 400 cc died, whereas three patients who received 500 cc recovered. Furthermore, patient A. H., who received 200 cc, had a more severe and protracted course than patient E. H., who received 500 cc. Death occurred on the seventh and the fourteenth day, respectively, in two cases and on the nineteenth day in the case of the patient who was operated on for a complicating pelvic abscess.

A prompt and marked diminution in the output of urine occurred in every instance. The longest duration of marked oliguria before the onset of diuresis and recovery was sixteen days. Slight but distinct icterus appeared in five of the seven patients and lasted for from five to fourteen days. When some urine was voided directly after the transfusion it invariably contained what was believed to be hemoglobin or its derivatives. The blood pressure was not elevated, and generalized edema appeared in two patients, but only after infusion of large amounts of saline and dextrose solutions.

The mechanism by which incompatible blood produces structural and functional damage of the kidneys and the hepatic lesions noted in some fatal cases is not clear. Bordley considered various explanations in his study. He said he felt that mechanical blockage of the renal tubules by the hemoglobin and hematin casts could not be held entirely accountable, though this view is held by some. He stated that the weight of evidence suggested that the anatomic and functional renal changes were produced by an unknown toxin resulting from the mixing *in vivo* of incompatible bloods. That hemoglobin itself may not produce anatomic or functional changes in the kidney was previously shown by Sellards and Minot<sup>7</sup> and by Bayliss<sup>8</sup>.

The necrosis of the liver noted in one of our fatal cases and in numerous other reports of necropsies is considered by some to be analogous to necrosis seen in other toxic states, for example, eclampsia. In view of the manifest relation to a hemolytic reaction, we wish to call attention to the extensive studies of Pearce<sup>9</sup> (1904-1906), in which he

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7 Sellards, A. W., and Minot, G. R. Injection of Hemoglobin in Man and Its Relation to Blood Destruction, with Especial Reference to the Anemias, *J. M. Research* **34** 469, 1916.

8 Bayliss, W. M. Is Haemolysed Blood Toxic? *Brit. J. Exper. Path.* **1** 1 (Feb.) 1920.

9 Pearce, R. M. The Experimental Production of Liver Necroses by the Intravenous Injection of Hemagglutinins, *J. M. Research* **12** 329 (July) 1904. Pearce, R. M., and Winne, C. K., Jr. Concerning Hemagglutinins of Bacterial Origin and Their Relation to Hyaline Thrombi and Liver Necroses, *Am. J. M. Sc.* **128** 669, 1904. Pearce, R. M. A Further Study of the Experimental Production of Liver Necroses with Injection of Hemagglutinative Sera, *J. M. Research* **14** 541, 1906.

dealt with identical hepatic necrosis induced in experimental animals by the the injection of serums rich in hemagglutinins. He believed that the lesions he observed were secondary to impaction of agglutinated red blood cells (with the formation of hyaline thrombi) in the hepatic sinusoids, shutting off the blood supply. These lesions were so easily produced and of such severity that he was able to use the method to induce a form of experimental cirrhosis<sup>10</sup>

While the ultimate cause of some of the manifestations must be considered as still unexplained, there can be little doubt that the syndrome is initiated by hemolysis of the donor's red blood cells. There is a striking similarity to the suppression of urine and uremia seen in cases of severe blackwater fever,<sup>4</sup> even with regard to the histopathologic changes in the kidneys.

Bordley<sup>1</sup> stated "In not a single case is there complete and satisfying evidence to prove that the blood of the donor was compatible with that of the recipient." In this regard he especially stressed the necessity for repetition of the cross-matching after the reaction has occurred. A review of our data and other recent reports<sup>11</sup> indicate that in some instances retyping and recross-matching failed to show any evidence of incompatibility. It seems from this that in rare instances serious hemolytic reactions may be unavoidable in the present state of knowledge of blood groups.

Our pathologic studies confirm the observations of Bordley and others and shed no new light on the problem of the pathogenesis of the lesions. It is worth reiterating that the essential lesions consist of tubular dilatation and some degeneration (particularly affecting the epithelium of Henle's loop and the distal convoluted tubule) with interstitial edema, a picture suggestive of mercurial nephrosis. The degree of tubular damage observed varies with the time of death. The distinctive feature is the formation of peculiar obstructing pigment casts in the distal tubular segments.

The changes observed in the tubules in both our fatal cases apparently represented late stages in the events following a hemolytic reaction.

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<sup>10</sup> Pearce, R. M. Experimental Cirrhosis of the Liver, *J. Exper. Med.* **8** 64, 1906.

<sup>11</sup> Parr, L. W., and Krischner, H. Hemolytic Transfusion Fatality with Donor and Recipient in the Same Blood Group, *J. A. M. A.* **98** 47 (Jan 2) 1932. Wildegans, H. Die Todesfalle nach Bluttransfusionen, *Deutsche med. Wchnschr.* **56** 2031 (Nov 28) 1930. Stewart, S. G. Acute Renal Insufficiency Following Blood Transfusion, *M. Clin. North America* **15** 553, 1931. McCandless, H. G. A Hemolytic Blood Transfusion Reaction with Oliguria, *J. A. M. A.* **105** 952 (Sept 21) 1935. DeGowin and Baldrige<sup>2b</sup>. Irsigler<sup>2c</sup>. Polayes and Lederer<sup>2d</sup>. von Deesten and Cosgrove<sup>2e</sup>. Johnson and Conway<sup>2f</sup>.



The first patient came to necropsy seven days after the transfusion had been given, and the finding of calcific casts in the renal tubules recalls similar changes in the advanced stages of mercurial nephrosis. The second patient died seventeen days after a transfusion, and while the presence of suppuration elsewhere may have played a rôle in the degenerative epithelial changes seen the persisting pigment casts are evidence of the effect of the hemolytic reaction.

The location of the peculiar casts in cases like these suggests that concentration of the urine and an increase in the hydrogen ion concentration at this point in the uriniferous tubule lead to precipitation of the hemoglobin and injury to the epithelial cells. Beyond Henle's loop the breakdown of hemoglobin continues with the formation of large, obstructing crystal masses of hematin, some embedded in epithelial and amorphous debris, causing dilatation of the tubules. This explanation was first suggested by Baker and Dodds<sup>12</sup> in their clinical and experimental observations. Studying the effects of hemoglobinuria in rabbits, they found that since the normal rabbit's urine is alkaline, no anatomic changes developed, nor were hemoglobin or hematin casts formed in the tubules. However, when the urine was rendered acid, the breakdown of hemoglobin could proceed, and lesions identical with those seen in the kidneys in blackwater fever or in posttransfusion nephrosis were demonstrated.

We have concluded that the peculiar eosinophilic casts present in the convoluted tubules and in the Henle loops contain hemoglobin or one of its degradation products, because of the color of these casts in unstained sections and their positive reaction with benzidine by Lepehne's<sup>5</sup> method for staining hemoglobin in histologic preparations.

#### CONCLUSIONS

Observations are reported on seven patients who sustained a severe hemolytic reaction following transfusion with incompatible blood, four recovered, and three died.

The reaction was characterized by the sudden onset of oliguria (in instances of severe involvement, anuria) and hemoglobinuria and the gradual development of renal insufficiency and uremia.

Mistakes in grouping accounted for the reaction in three patients. In two, failure to recheck the grouping after the transfusion left doubt as to the classification; in two, regrouping showed the bloods of the donor and recipient to be of the same group. In the latter two patients the reaction was unpredictable and therefore, in the present state of

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<sup>12</sup> Baker, S. L., and Dodds, E. C. Obstruction of the Renal Tubules During the Excretion of Haemoglobin, *Brit. J. Exper. Path.* 6: 247, 1925.

knowledge of blood groups and methods for their identification, must be considered unavoidable

Pathologic observations in two of the three fatal cases revealed a necrotizing process affecting the uriniferous tubules which was like that seen in mercurial nephrosis. Distinctive pigment casts containing hemoglobin or its derivatives were conspicuous, and interstitial edema increased the size of the kidneys. Central focal necrosis was observed in the liver of one patient.

# HYPERPARATHYROIDISM COMPLICATED BY HYPERTHYROIDISM

REPORT OF A CASE

JOHN F NOBLE, M D

AND

JOSEPH F BORG, M D

ST PAUL

Hyperparathyroidism, long recognized as osteitis fibrosa cystica of von Recklinghausen, has become a well recognized clinical entity. Through the researches of such investigators as Hunter<sup>1</sup> and Jaffe,<sup>2</sup> stimulated by the observations of Mandl,<sup>3</sup> and from the numerous reports that have been published, the usual manifestations of this disease are now common knowledge to the clinician. The onset of the condition is insidious, and the symptomatology is so vague that until recently in most instances the patient with hyperparathyroidism has gone with the condition undiagnosed for many years. The clinical diagnosis is made, as a rule, only after the development of bony deformities or pathologic fractures. The case presented here is no exception to the rule, but because of certain unusual features it seems worthy of being reported.

The unusual features in this case were the associated hyperthyroidism, the rapid development of the clinical picture and the almost complete restoration of the atrophied bone, together with complete recovery after the removal of a parathyroid adenoma.

## REPORT OF CASE

*History*—The patient, an unmarried woman aged 33, was admitted to the Ancker Hospital on May 19, 1933, complaining of a fracture of the right wrist which was sustained after a trivial injury. An x-ray plate of the wrist had been made by the family physician, and he had referred her to the hospital because of the peculiar atrophy of the bones of the wrist and forearm which was revealed. The patient stated that she had not been entirely well since an attack of acute cystitis in 1931. In August 1932 she had an attack of abdominal pain with jaundice which was diagnosed as due to acute cholecystitis. She recovered from this attack after

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From the Ancker Hospital, St Paul, the Department of Medicine and the Department of Pathology, the University of Minnesota, Minneapolis

1 Hunter, D. *Lancet* **1** 897, 1930

2 Jaffe, H. L. Hyperparathyroidism (Recklinghausen's Disease of Bone), *Arch Path* **16** 63 (July) 1933

3 Mandl, F. *Zentralbl f Chir* **53** 260, 1926, quoted by Hunter<sup>1</sup>

an illness of about a month, with only residual fatigability. In November 1932 pain began to develop in the calves of the legs, and weakness was noted in the lower extremities. These symptoms did not respond to symptomatic treatment. In January 1933 the patient consulted a dentist, who advised the extraction of several teeth. While this was being carried out, a large piece of the alveolar process of the mandible came away with the teeth. The dentist recognized the abnormal condition of the bone and advised the patient to consult a physician. She continued to work, however, until May 19 when she sustained a fracture of the wrist and forearm. During the period between January and May the pains in the legs and the weakness had become progressively worse, and the patient was conscious of an unnatural irritability. Her weight in 1931 was 145 pounds (66 Kg), and she considered this to be normal. When admitted to the hospital she weighed 116 pounds (52.6 Kg).

The patient had a tonsillectomy in 1914. In 1918 she was acutely ill with influenza, and the following year she had a febrile illness of six weeks' duration which was diagnosed as due to endocarditis. In 1923 a tuberculous appendix was removed. The patient was subject to repeated acute infection of the respiratory tract.

*Examination*—Physical examination showed the patient to be normally developed. She was intelligent and cooperative. There was evidence of a loss of weight, and the skin and mucous membranes were notably pale. There was no lymphadenopathy. The mouth was edentulous, the alveolar processes were larger than normal, but the mucous membrane over them was intact. There was a small, tender swelling over the eighth rib on the left side in the anterior axillary line. The heart and lungs were essentially normal. The blood pressure was 180 systolic and 110 diastolic. Examination of the abdomen revealed no abnormality but an appendectomy scar. The reflexes were hyperactive, but the muscle tone was poor. There was definite diminution of muscular irritability to electrical stimulation. The Colles fracture had been well reduced and immobilized. There was a diffuse swelling over the middle third of the left tibia.

Roentgenologic examination of the skeleton in May 1933 showed marked osteitis fibrosa cystica involving all the bones. The process was most pronounced in the left forearm, the long bones of the lower extremities, the ribs and the skull. The most advanced lesions were seen in the bones of the left forearm, where there was a pathologic fracture of the lower end of the radius. Both the radius and the ulna showed marked generalized decalcification of a coarse, irregular type. This was most pronounced at the site of the fractures in the left forearm and in the middle third of the left radius, where there was cystic expansion of the cortex. The periosteum of these bones was thickened and calcified. On June 17 a roentgenogram of the same region showed the decalcification to be much more advanced. In the carpal bones a similar process of decalcification, which had not been previously seen, was demonstrated. On July 10 further resorptive changes of the left radius and ulna were noted. The cystic area of the radius showed almost no calcium, and the cyst had increased in size (fig 1). Many of the ribs showed decalcified, fusiform cystic swellings (fig 2). The skull was thicker than normal, but both the inner and the outer table were thinned out, the cancellous portion of the bone showing an irregularly mottled appearance. At several points regular, almost circular cystic defects were seen in the skull (fig 3). The tibiae and fibulae showed an advanced degree of decalcification, which was fairly well limited to the shafts of the bones. The periosteum of these bones showed the

most marked involvement (fig 4) The same process was seen in the femurs, but here the lesion was limited to the middle third of the bone The pelvis and spine showed the least involvement

The flat bones are said (Jaffe<sup>2</sup>) to be involved more frequently than the short tubular bones, but in this case the pelvis showed less involvement than the metacarpal bones

TABLE 1—*Laboratory Data*

Date	Blood Calcium, Mg per 100 Cc	Blood Phosphorus, Mg per 100 Cc	Calcium in Urine, Gm in 24 Hrs	Hemoglobin, %	Erythrocytes	Leukocytes	Blood Sedimentation Mm
5/28/33	18.0			60	3,300,000	12,500	101
6/ 1/33	16.5		0.980				
6/ 2/33		3.6	0.150				
6/ 3/33			0.200				
6/ 5/33			0.430				
6/ 6/33			0.280				
6/ 7/33		2.4	0.110				
6/ 8/33	19.4		0.330				
6/ 9/33	15.0	2.4	0.670				
6/13/33	14.2	2.4	0.150				
6/14/33	14.0		0.220				
6/15/33	14.5	2.6	0.600				
6/19/33			0.310				
6/20/33	14.8	2.3	0.540				
6/22/33			0.400				
6/23/33			0.660				
6/24/33			0.360				
6/25/33			0.680				
6/26/33	16.8	2.0	0.740				
6/28/33	14.5	2.2	0.140				
6/29/33			0.350				
6/30/33			0.370				
7/ 1/33			0.640				
7/24/33	8.2			38	2,180,000	8,950	
7/25/33			0.028				
7/26/33	8.8	2.2	0.090				
7/27/33	8.1	2.1		38	2,400,000	7,700	
7/28/33	6.0						
7/29/33	6.7	2.3					
7/31/33	6.0						
8/ 1/33	7.0	2.6					
8/ 2/33	7.0	2.7					
8/ 3/33	7.2						
8/ 4/33	7.4						
8/ 5/33	7.5	2.8					
9/ 7/33	7.5	2.8					
8/ 8/33	7.0			30	2,430,000	7,600	
8/11/33	7.5	2.7		34	2,800,000	7,500	
8/14/33	8.2		0.020	36	2,980,000	7,000	
9/15/33	8.3	2.8	0.016				
8/17/33	8.2		0.014				
8/18/33	8.1		0.081				
8/21/33	8.0		0.080	42	2,940,000	5,650	
8/23/33	8.5			52	3,130,000	7,100	
9/ 6/33	8.9		0.020	54	3,320,000	7,900	
9/19/33	8.2	3.2		54	3,550,000		
10/ 5/33	10.0			54	3,370,000	9,850	
10/16/33	10.0	3.4		53	3,780,000	10,400	25
10/23/33	9.6			64	3,800,000	6,600	
11/ 1/33	10.2			68	3,860,000	9,650	37
11/15/33	9.6			72	4,100,000	12,500	
12/ 2/33	9.4			80	4,450,000	12,600	
5/22/34				83	4,580,000	7,900	

The most pertinent laboratory findings are summarized in table 1 Before operation the calcium content of the blood was persistently high Immediately after operation there was a sharp drop in the calcium content to a point well below normal Subsequently the calcium content gradually assumed a normal level These findings will be discussed later The phosphorus content of the blood (table 1) was within normal limits After operation the readings were

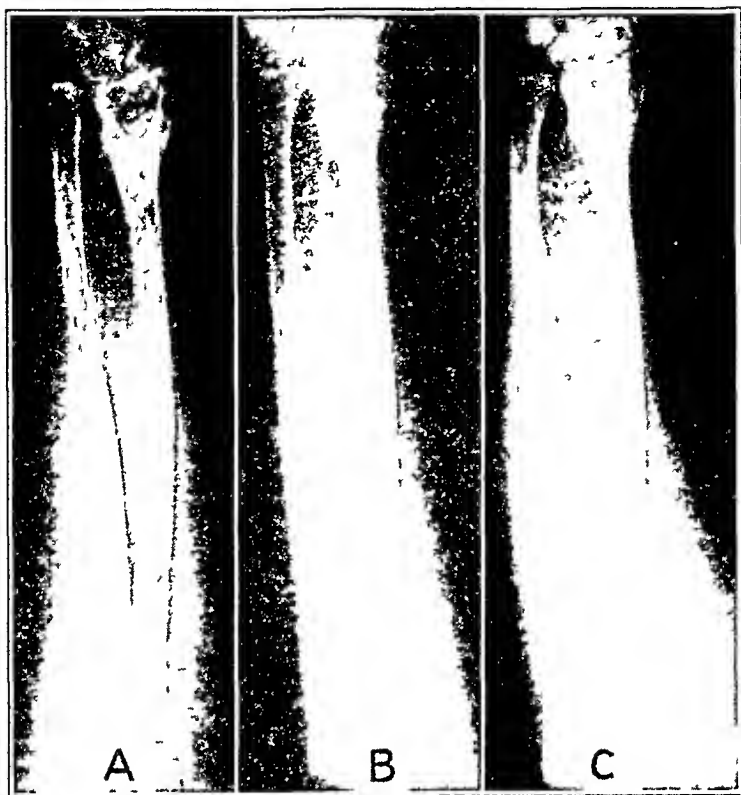


Fig 1—*A*, the left radius and ulna, showing marked osteitis fibrosa cystica (May 23), *B*, seven weeks postoperatively, showing marked recalcification, *C*, five months later, showing complete restoration of the bone



Fig 2—*A*, a roentgenogram showing cystic areas in the ribs (May 23), *B*, four months later, showing marked recalcification

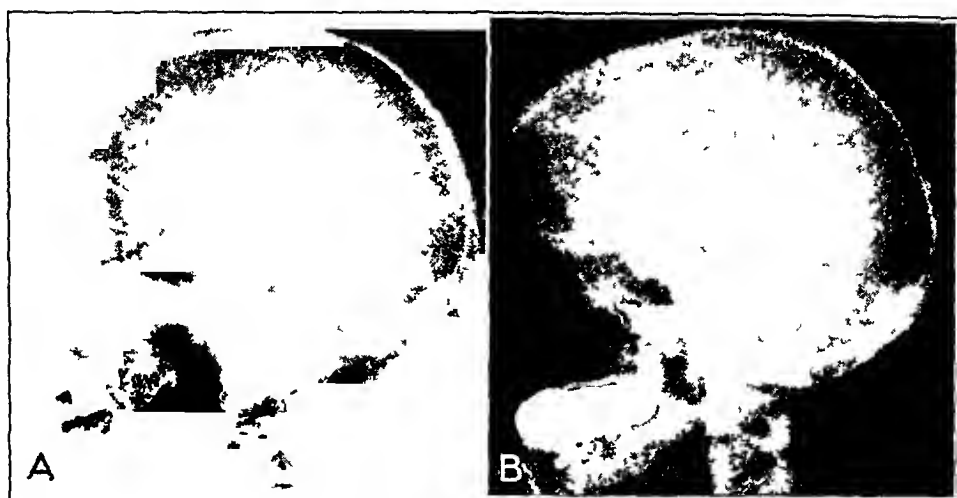


Fig 3—*A*, a roentgenogram showing the punched-out areas of the skull, with thickening of the tables (May 23), *B*, five months later, showing recalcification and restoration of tables of the skull

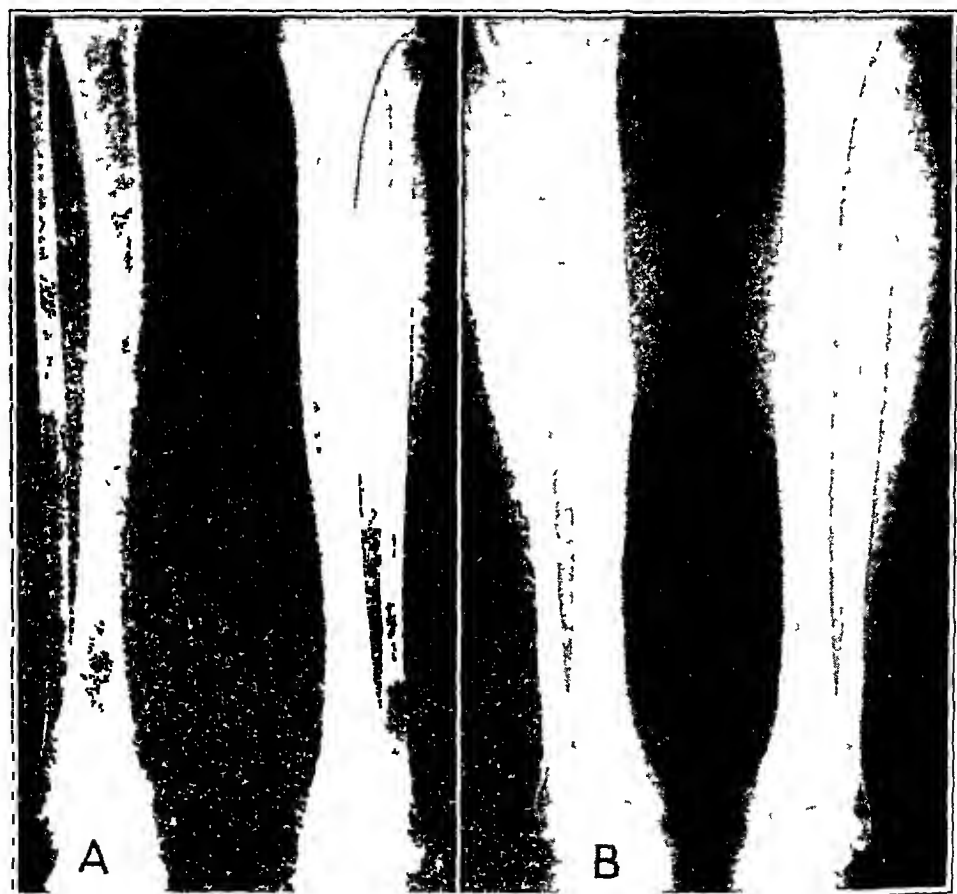


Fig 4—*A*, typical osteitis fibrosa cystica of both femurs and tibias (May 23), *B*, five months later

somewhat higher, however. Numerous determinations of the amount of calcium excreted in the urine were made while the patient was taking a diet containing 0.5 Gm of calcium a day, and the results are shown in the same table. The hemoglobin value and the erythrocyte count also are recorded in table 1. The phenol-sulfonphthalein elimination was 18 per cent in the first hour, 8 per cent in the second hour and 12 per cent in the third hour. Bence-Jones' protein was not found in the urine. The urine occasionally showed a trace of albumin, and the specific gravity in specimens examined as a routine showed a tendency to be fixed at a low level, the readings ranging between 1.004 and 1.010.

While the patient was being observed in the hospital she was comfortable, but she complained of increasing muscular weakness. The weight decreased to 99 pounds (50 Kg). The pulse rate was rapid, ranging from 90 to 120 per minute. Because of the persistently rapid pulse rate, a determination of basal metabolism was made on June 23. The reading was +38 per cent. This test was repeated on three successive days, and the readings were +43 per cent, +38 per cent and +30 per cent, respectively. The patient was given 10 drops of compound solution of iodine three times a day, and on July 11 the basal metabolic rate was +11 per cent. The increased metabolic rate, the rapid pulse, the hyperactive reflexes and the loss of weight, together with the therapeutic response to compound solution of iodine, indicated the presence of complicating hyperthyroidism. During the period of observation between May 19 and July 11 rapidly progressive decalcification, as indicated by roentgenograms, was observed.

*Operation*—Dr A. R. Colvin was called in surgical consultation at that time, and an operation was performed on July 21. A thorough exploration for parathyroid tissue was carried out without success. In view of the clinical picture of hyperthyroidism, it was deemed advisable to perform a subtotal thyroidectomy. It was hoped that at the same time some parathyroid tissue might be removed. The entire left lobe of the thyroid gland, together with the posterior capsule, was therefore resected, and a portion of the right lobe, including a small adenoma, also was excised. Further exploration of the base of the neck and the superior portion of the mediastinum revealed a cystic mass, about 4 by 2 cm in diameter, behind the manubrium of the sternum. This cyst was ruptured during removal, and brownish fluid escaped. The solid portion of the tumor was yellowish brown, and its gross appearance was suggestive of parathyroid tissue. This impression was confirmed by microscopic section.

*Pathologic Report*—The tissue received in the laboratory consisted of several pieces of thyroid gland weighing 28 Gm. One piece appeared to be a complete lobe of the thyroid gland. On incision this tissue showed a uniform glossy surface the appearance of which did not suggest hyperplasia. There were no adenomatous nodules present here and nothing recognizable as parathyroid tissue. A second irregular piece of thyroid tissue of similar appearance, apparently representing a portion of a lobe, also was present. The specimen included a third piece of tissue, which proved to be a well defined thyroid adenoma about 2 cm in diameter. On section the surface of this nodule showed the presence of colloid, but no evidence of hyperplasia was seen. The fourth piece of tissue appeared to be a collapsed cyst, the diameter of which when distended was estimated to have been 4 by 2 cm. The cyst was unilocular, and most of its wall was thin, fibrous and translucent. Forming one wall of the cyst was a mass of fleshy tissue measuring about 3 by 2 cm. On section the surface of this tissue was found to be yellowish brown, homogeneous and friable. The tumor proved to be a cystic parathyroid adenoma.



Microscopic sections of the parathyroid tissue (fig 5), stained with hematoxylin and eosin, showed it to be composed for the most part of clear (*wasserhelle*) cells arranged in sheets and supported by a fine reticulum of connective tissue. These cells were polyhedral and showed well demarcated membranes, giving large areas of the tumor a mosaic appearance. The cytoplasm of these cells was clear or slightly foamy, and the nuclei were round and vesicular, showing prominent nucleoli. There were some large pyknotic nuclei and occasionally a multinucleated cell. Numerous irregular mitoses were seen in these cells. Only a few oxyphilic cells were seen, usually occurring singly or in small groups. They were somewhat larger than the clear cells and more irregular in outline. The cytoplasm was pink staining and granular, and the nuclei were somewhat larger than those of the clear cells. The chromatin of the nuclei was more compact, no nucleoli were seen. Cells of a third type occurred in dense clumps or occasionally

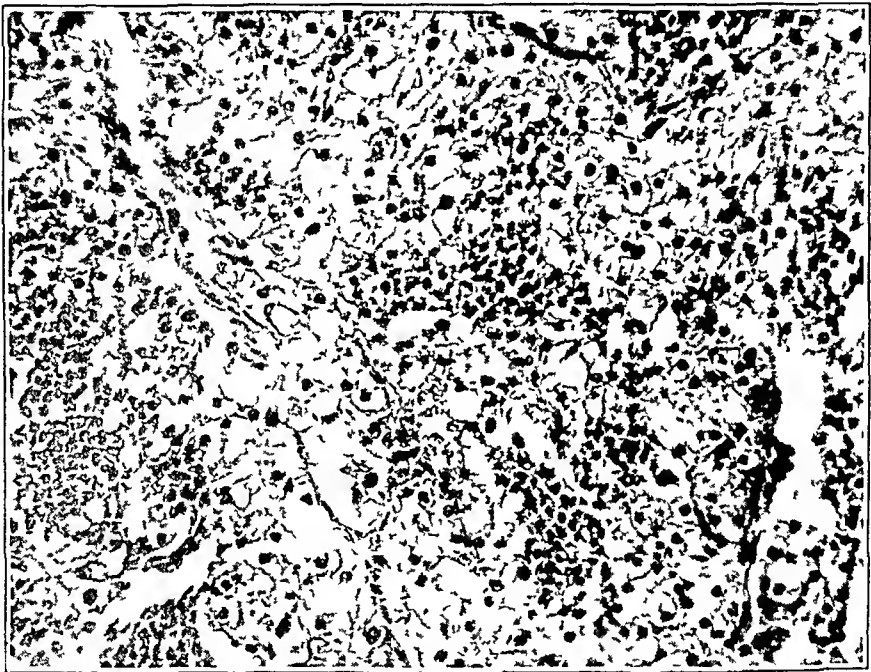


Fig 5—Microscopic section of the parathyroid adenoma

formed regular columns or strands. The cytoplasm of these cells was not prominent, but each nucleus was small, dense and deep staining and was situated at the base of the cell. This undoubtedly was the principal type of cell. Transitions between this cell and the well formed *wasserhelle* cell were present at certain points. There was no evidence of invasion of the capsule of the adenoma by any of the three types of cell, and while the tumor appeared to be rapidly proliferating, there was no evidence of malignancy.

Microscopic sections of the thyroid gland showed that the acini varied considerably in size. They all contained colloid material which had a normal staining reaction. The height of the epithelium lining these acini was practically normal, and no evidence of hyperplasia was seen. In the stroma of the gland, however, definite collections of lymphocytes were seen. The presence of the lymphocytes was the only residual histologic evidence of the hyperplasia of the thyroid gland, which must have been present before treatment with iodine was instituted.

The predominant cell in the parathyroid tissue, as shown in figure 5, was the *wasserhelle* cell. According to the classification of Castleman and Mallory,<sup>4</sup> the parathyroid lesion belonged to the neoplastic group. The diagnosis, therefore, was clear cell cystic adenoma of the parathyroid gland.

*Course*—The patient withstood the operation well, but on the fourth post-operative day, July 25, marked muscular hyperirritability was noted, and a positive Trousseau sign developed. The calcium content of the blood on July 24 dropped to 8.2 and later (July 28) to 6 mg per hundred cubic centimeters. Large doses of calcium and parathyroid extract were given, and the symptoms of tetany were promptly controlled. The dose of parathyroid extract was gradually decreased, and the medication was discontinued after ten days, with no recurrence of the symptoms. During this period increasing pallor was noted, and on August 8 the hemoglobin reading was 30 per cent. The anemia was treated with large doses of iron and ammonium citrates, with no improvement until intramuscular injections of liver extract were given. These were continued during the remainder of the patient's stay in the hospital, with the resulting improvement shown in table 1. In addition, calcium lactate, viosterol and heliotherapy (quartz mercury vapor lamp) were used, and a gradual improvement was noted in the patient's general condition. The pulse rate decreased, the appetite improved and there was a gain in weight.

On July 25, four days after the operation, the calcium content of the urine showed the first drop to a point below normal. This low content persisted until September 6, after which no further determinations were made. The studies of the calcium content of the blood showed a gradual increase from the low reading of 6 mg per hundred cubic centimeters on July 28 to a normal figure. The first normal figure was not obtained, however, until October 11. The patient was discharged from the hospital on August 21. She continued to take calcium lactate, viosterol and iron and ammonium citrates, the taking of liver extract being discontinued.

After leaving the hospital the patient continued to gain rapidly in weight and strength. In September and October, however, the hemoglobin value became stationary at 54 per cent. Liver extract was again given, and (table 1) there was a rapid rise in the hemoglobin value to 80 per cent. On November 1 the basal metabolic rate was normal. The phosphorus content of the blood, which had never been low, showed a gradual rise. The last reading (September 6) was 3.4 mg per hundred cubic centimeters of blood. Three months after leaving the hospital the patient had gained 40 pounds (18 Kg) in weight and had returned to work, feeling better than she had in years.

Roentgenograms of the left forearm were taken at short intervals to follow the process of recalcification. These films showed beginning deposition of calcium as early as sixteen days after the operation. The first and most rapid deposition occurred in the large cystic area of the radius, which had been almost completely decalcified. Later, there was a remarkable restoration not only of the calcium content of the involved bones but also of their architecture. These changes proceeded rapidly until December 21, when the bones presented a normal appearance, save for a densely calcified cystic area and a well calcified callus in the region of the fracture. Recalcification of the balance of the skeleton showed corresponding improvement. The accompanying illustrations (figs 1 to 4) show the conditions at that time. Roentgenograms taken in March 1935 showed even greater improvement.

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4 Castleman, B, and Mallory, T B. *Am J Path* 11 1, 1935

TABLE 2—Summary of the Cases Reported in the Literature

Authors	Year	Age of Patient, Years	Sex	Type of Parathyroid Tissue Removed	Duration of Symptoms Before Diagnosis	Basal Metabolic Rate	Length of Time Patient Was Followed	Degree of Recalcification of Bone	Clinical Result
Boyd, J. D., and Mulgram, J. A. M. A. 93, 684, 1929	1929	21	M	Normal and cystic degeneration Adenoma	3 1/2 yr		2 mo	None	Improved
Barr, D. P., Bulger, H. A., and Dixon, H. H. J. A. M. A. 92, 951, 1929	1929	56	F	Adenoma	8 yr				Improved
Wilder <sup>10</sup>	1927	32	F	Adenoma	6 yr	+12, +2	4 mo	Moderate	Improved
Snapper, I. Arch Int Med 46, 506, 1930	1930	56	M	Adenoma	7 yr		9 mo		Improved
McOellian and Hannon <sup>13</sup>	1930	30	M	Tumor	8 yr	-8, -17	13 yr	None	Died
Ballin and Morse <sup>11c</sup>	1931	50	M	Parathyroid hyperplasia	10 yr				Died
	1931	17	M						Died
	1931	65	M	3 parathyroid glands	3 yr <sup>a</sup>		4 mo	Moderate	Improved
	1931		M	2 parathyroid glands,	1 yr	+25	5 mo		Improved
	1931	63	F	with cystic degeneration Adenoma					Improved
Schnabel, T. G. M. Clin North Amerien 14, 977, 1931	1930	26	M	No operation	5 yr		1 mo		Improved
Tavener, J. L. Minnesota Med 16, 269, 1933	1933	53	F		8 yr				Unimproved
Struthers, J. W. Edinburgh M. J. 40, 37, 1933	1933	47	M	Adenoma	5 yr				Died
	1933	38	F	Parathyroid hyperplasia	10 yr		?		Died
	1933	48	F	Adenoma	? yr				Died
Rankin, F. W., and Priestley, J. W. Am J Surg 20, 298, 1933	1933	34	F	Thyroid adenoma, lobectomy	3+ yr	+12, +21	4 mo	Slight	Improved
	1933	47	F	Adenoma	4 yr		3 mo	None	Died
	1933	42	F	Tumor	10 yr		2 yr	None in 6 mo, definite	Improved
	1933	26	F	Tumor	2 yr		9 mo	In 2 yr, Definite	Improved
	1933	23	F	Tumor	8 yr	-22	16 mo	None in 5 mo, definite	Improved
Cohen, H., and Kelly, R. E. Brit J Surg 20, 472, 1933	1933	48	F	Tumor (principal cell)	9 yr		3 mo	In 16 mo, Moderate	Improved
Rosedale, R. S. Am J Path 8, 745, 1932	1932	50	F	Tumor	7 yr		4 days		Died
Hitzrot, L. H., and Comroe, E. L. Arch Int Med 50, 317, 1932	1932	42	F	3 normal parathyroids, thyroidectomy	4 yr	+11	5 mo	None in 3 wk, improved in 9 wk	Improved
Comper, E. L. Surg., Gynec. & Obst 50, 783, 1930	1930	59	F	Adenoma	5 yr		5 mo	None	Improved
Gold, L. Mitt. d. Grenzgeb. d. Med. u. Chir 61, 63, 1928	1928	54	F	Adenoma			1 mo		Improved
Barr, D. P., and Bulger, H. A. J. M. Sc 170, 449, 1930	1930	38	M	Parathyroid hyperplasia	2 yr		2 mo		Improved
	1930	46	F	Parathyroid hyperplasia	2 yr			None	Died, no operation

Ball 12	1930	50	M	None found	7 yr	+17, +27, +1% (iodine therapy)	None	Unimproved
Pemberton, J, and Geddle, B Am J Surg 92:202, 1930	1930	14	F	Tumor	16 mo		None	Improved
Wendeliss Thomason, G, and Smith, L West J Surg 41:78, 1933	1930 1933	17 41	M F	Parathyroid hyperplasia Adenoma	1 yr 18 mo	3 mo	None	Improved Improved
Noble, T P J Bone & Joint Surg 14:181, 1932	1932	40	M	Adenoma	3 1/2 yr	3 days	None	Died
Cooley, T B Tr Am Pediat Soc 43:20, 1931	1931	14	F	Cystic parathyroid gland	1 yr	+23	Doubtful	Improved
Abel, A L Thomson, G, and Hawksley, L M Lancet 2:525, 1933	1933	58	F	Adenoma	2 yr	1 yr	Slight in 7 mo, definite in 13 mo	Improved
Churchill, F D, and Cope, O Surg, Gynec & Obst 58:253, 1934	1934	46	F	Parathyroid tumor	3 yr 4 yr 5 yr	6 mo 13 mo 1 yr	Definite	Improved Improved Improved
	1934	60	F	Parathyroid tumor	3 yr	6 mo	Marked	Improved
	1934	13	F	Parathyroid tumor	1 yr	3 1/2 yr	None	Improved
	1934	41	F	Parathyroid tumor	2 yr	2 mo	None	Improved
	1934	55	F	Parathyroid tumor	13 yr	3 mo	None	Improved
	1934	36	F	Parathyroid tumor	3 yr	Few days		Died
	1934	44	F	Parathyroid tumor	1 yr			
	1934	33	M	Parathyroid tumor	1 yr			
	1934	54	F	Parathyroid tumor	13 yr			
	1934	53	F	Parathyroid tumor	3 yr			
	1932	25	F	Adenoma				
Babcock, W W S Clin North America 12:1387, 1932	1933	24	M	Cystic tumor	7 yr	4 mo	Definite	Improved
Keynes, G, and Taylor, H Brit J Surg 21:20, 1933	1931	25	F	Adenoma	1 yr	6 mo	Definite	Improved
Chervitz, O, and Olsen, H C Hos pitalstid 7:1, 1932	1932	42	F	Adenoma	5 yr	5 wk	Slight	Improved
Helstrom, J Acta chir Scandinav 69:237, 1932	1932	44	F	Adenoma	5 yr	5 wk	Slight	Improved
Morton, J J Internat Clin 3:18, 1933	1933	20	F	Clear cell adenoma		+9		Improved
Beck, A Arch f klin Chr 152 123, 1928	1928	41	F	Tumor	9 yr			
Albright, F, Aub, J C, and Bauer, W J A M A 102:1276, 1934	1934	46	F	Tumor	14 yr		Moderate	Improved
	1934	60	F	Tumor	3 1/2 yr		Increased	Improved
	1934	13	F	Tumor	4 yr			Improved
	1934	41	F	Tumor	5 yr			Improved
	1934	55	F	Tumor	5 yr			
	1934	35	M	Tumor	15 yr			Died
	1934	36	F	Tumor	3 yr			Improved
	1934	44	F	Tumor	1 1/2 yr			Improved
	1934	33	M	Tumor	2 yr			Improved
	1934	54	F	Tumor	39 yr			Improved
	1934	53	F	Tumor	12 15 yr			Improved
	1934	51	F	Tumor	9 yr			
	1934	22	M	Tumor	1 yr			Improved
	1934	52	M	Tumor	1 yr			
	1934	62	F	Tumor	7 yr			
	1934	26	M	Tumor	1 1/2 yr			
	1934	55	F	Tumor	1 1/2 yr			

TABLE 2—Summary of the Cases Reported in the Literature—Continued

Year	Authors	Age of Patient, Years	Sex	Type of Parathyroid Tissue Removed	Duration of Symptoms Before Diagnosis	Basal Metabolic Rate	Length of Time Patient Was Followed	Degree of Reossification of Bone	Chemical Result
1934	Bergstrand, H Am J Cancer 21 581, 1934	64	F	Adenoma	2 yr				Died, no operation
1934	Gutman, A B, Swenson, P C, and Parsons, W B J A M A 103 87, 1934	34	M	Adenoma	2 yr	+3	4 mo	Definite	Improved
1934		53	F	Adenoma	10 yr	+22	6 wk	Definite	Improved
1934		35	F	Adenoma	16 yr				Died
1934		60	F	Adenoma	2 yr	+5			Died, no operation
1935		42	F	Adenoma					Died, no operation
1929	Godel, A Wien klin Wchnsehr 38 246, 1925	29	F	Adenoma (malignant)		-4			Improved
1937	Guy, C O Surg, Gynec & Obst 48 557, 1929	39	M	Adenoma					Died, no operation
1971	Hand, J R S Clin North America 15 1365, 1971	40	F	Adenoma	2+ yr				Died, no operation
1971	Berner, D Vichows Arch f path Anat 282 680, 1971		F	Tumor	2+ yr				Died, no operation
1932	Hanke, H Arch f klin Chir 172 366, 1932	33	F	Adenoma	7 yr				Died, no operation
1932	Mertz, A A Illinois M J 62 468, 1972	49	F	Adenoma	6 yr				Died, no operation
1932		70	F	Adenoma	8 yr		3 mo	Definite	Improved
1932		64	F	Adenoma	8 1/2 yr			Progressive	Improved
1932		77	F	Adenoma	20 yr		8 days		Improved
1972		73	F	Adenoma	1 yr				Improved
1934		14	M	Adenoma	6 mo		8 mo	Marked	Improved
1929	Mumpriss, T W and Butler, R W Brit J Surg 21 500, 1934	41	F	Adenoma	3 yr				Improved
1931	Hunter, D Price Roy Soc Med 23 27, 1929	31	M	Tumor	2 yr				Improved
1931	Allen, F N Proc Staff Meet, Mayo Clin 6 684, 1931	47	F	Tumor	10 yr			Definite	Improved
1935	Strandgaard, H Hospitalstid 77 383, 1934	62	F	Adenoma	5 yr	+20	6 mo		Improved
1935	Lahey, F H, and Haggart, G L Surg, Gynec & Obst 60 1033, 1935	50	F	Adenoma	5 yr		15 mo		Improved
1935		74	F	Adenoma	6 yr		18 mo		Improved
1935		44	F	Adenoma	2 yr	+14	3 1/2 yr		Improved
1935		52	F	Adenoma	8 yr		8 mo		Improved
1931	Hunter, D Brit J Surg 19 203, 1931	49	F	Parathyroid hyperplasia					Died
1931		37	F	Tumor	5 yr		10 mo		Improved
1931		49	F	Parathyroid hyperplasia	8 yr		10 mo		Improved
1931		61	F	Tumor	1 yr		5 mo		Improved

The relatively short period in which symptoms were presented prior to the diagnosis in this case led to an investigation of the duration of the clinical course in ninety-six cases reported in the literature which was available for study to the early part of 1934 (table 2). It is difficult to determine with accuracy the date of onset of a disease which appears so insidiously. However, for practical purposes, the time of appearance of the most common symptom, pain in the legs, or of bony deformity may be considered to represent the time of onset. In the forty-nine cases in which such information was available, it could be ascertained that the disease had an average duration of four and eight-tenths years from the onset until it was recognized clinically. While it may be granted that some of these cases would have been recognized earlier had the disease been better known, it is of interest that the shortest duration reported was eighteen months. In the present case the duration of symptoms was only six months. The markedly progressive decalcification demonstrated in this case during the short period of observation before operation is noteworthy. The progress was so rapid as to indicate the probable presence of an added decalcifying factor in this case.

The studies of Aub, Bauer, Heath and Ropes<sup>5</sup> have shown that in hyperthyroidism there is marked disturbance of the calcium metabolism, as evidenced by decalcification of bone. This picture of bone decalcification, which is sometimes so severe as to cause spontaneous fracture, has been described also by Krummer,<sup>6</sup> Bernard,<sup>7</sup> Plummer and Dunlap,<sup>8</sup> von Recklinghausen<sup>9</sup> and Hunter.<sup>1</sup> Aub and his colleagues<sup>5</sup> have shown that in hyperthyroidism there is an increase in the fecal excretion of calcium, in contradistinction to hyperparathyroidism, in which there is a marked increase in the urinary excretion of calcium and a normal or decreased fecal excretion. These investigators have demonstrated that there is a diminished excretion of calcium in myxedema, and they state the belief that hyperthyroidism directly affects osseous catabolism and is independent of any effect of the parathyroid gland on bone. The calcium content of the blood in the two diseases also differs. In hyperthyroidism the calcium content is normal, while in hyperparathyroidism it is almost always elevated, Wilder's<sup>10</sup> patient offering the only exception.

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5 Aub, J. C., Bauer, W., Heath, C., and Ropes, M. *J. Clin. Investigation* **7** 97, 1929.

6 Krummer, R. H. *Rev. méd. de la Suisse Rom.* **37** 439, 1917, quoted by Hunter.<sup>1</sup>

7 Bernard, F. *München med. Wchnschr.* **74** 432, 1927.

8 Plummer, W. A., and Dunlap, H. F. *Proc. Staff Meet., Mayo Clin.* **3** 119, 1928.

9 von Recklinghausen, F., in *Festschrift für Rudolf Virchow*, Berlin, George Reimer, 1891, quoted by Hunter.<sup>1</sup>

10 Wilder, R. L. *Endocrinology* **13** 231, 1929.

From a study of the ninety-six case reports it is difficult to determine the frequency of the association of hyperthyroidism and hyperparathyroidism. In only twelve instances was the basal metabolic rate mentioned. In eight of these cases the readings were normal. In three cases<sup>11</sup> the basal metabolic rate was increased, the readings being +22, +23 and +25 per cent, respectively, but no further mention of the significance of these findings is made. In the fourth case, reported by Ball,<sup>12</sup> the patient presented the clinical picture of hyperparathyroidism. An adenoma of the thyroid gland was present, and basal metabolic rates of from +15 to +27 per cent were recorded. By means of iodine therapy the rate was reduced to +1 per cent. Subtotal thyroidectomy was performed, but no parathyroid tissue was found. The symptoms referable to hyperthyroidism were improved, and the basal metabolic rate dropped to +12 per cent, but the picture of hyperparathyroidism continued unchanged. In the first case of hyperparathyroidism reported in this country, by McClellan and Hannon,<sup>13</sup> the basal metabolic rate was normal both before and after resection of normal parathyroid tissue. Later a parathyroid adenoma was found and resected. In the case reported here it is felt that the element of hyperthyroidism definitely influenced the rapidity of the course and that the removal of the thyroid gland as well as of the parathyroid adenoma influenced the rapidity and the degree of recovery.

In the series of case reports studied the postoperative results were for the most part inadequately given, especially with reference to the improvement of the condition of the bones. In only twenty-four of the ninety-six cases were results reported. In thirteen of these cases evidence of recalcification was noted at periods of from one month to two years. In four of the cases in which normal parathyroid tissue was removed no improvement was noted (table 2). From these figures it appears that recalcification of bone seldom occurs within several months after the removal of parathyroid tissue. In the case reported here evidence of recalcification was noted as early as the sixteenth day after operation.

As previously mentioned, the diagnosis of hyperthyroidism was suspected in this case because of the rapidity of the pulse rate, the loss of weight and the subjective symptoms of irritability in the absence of the objective signs of tremor and restlessness usually seen in a patient with a basal metabolic rate as high as that recorded here. Since calcium is known to have an inhibitive effect on many nervous symptoms,

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11 (a) Wendel, N. *Deutsche Ztschr f Chir* **228** 551, 1930. (b) Cooley, T. B. *Tr Am Pediat Soc* **43** 20, 1931. (c) Ballin, M., and Morse, P. F. *Am J Surg* **12** 403, 1931.

12 Ball, R. G. *Proc Staff Meet, Mayo Clin* **5** 331, 1930.

13 McClellan, W. S., and Hannon, R. R. *J Clin Investigation* **8** 249, 1930.

the absence of these signs might be explained by the fact that the high concentration of calcium in the serum had a sedative effect

This patient, like many of those reported on in the literature, showed a severe grade of secondary anemia. In view of the extensive damage to the bone marrow, it is reasonable to suppose that the relationship was one of cause and effect. This theory was supported by the fact that the anemia improved concurrently with the repair of the bony architecture, though the process seemed to be hastened by the administration of iron and liver extract.

#### SUMMARY

A case of hyperparathyroidism characterized by rapid decalcification and recalcification of bone is reported. The patient has remained in good health for two years after removal of a parathyroid adenoma. The picture was complicated by hyperthyroidism the presence of which is believed to have influenced the course of the disease.



# CLINICAL SIGNIFICANCE OF THE CHOLESTEROL PARTITION OF THE BLOOD PLASMA IN HEPATIC AND IN BILIARY DISEASES

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As early as 1862, Austin Flint Jr<sup>1</sup> described what he considered to be "a new excretory function of the liver consisting in the removal of cholesterine from the blood and its discharge from the body in the form of stercorine" At this early date he had already attempted to differentiate by means of the level of the cholesterol in the blood the jaundice "dependent upon the obstruction of the bile in the one case and its suppression in the other" Not much could be done further, because the methods of extracting and estimating the pure cholesterol from the various body fluids were difficult and tedious

In recent years interest in the relationship of the liver to cholesterol metabolism has been renewed The impetus has come from the development of newer and more accurate methods for the determination of cholesterol in the blood, body fluids and tissues, especially since the work of Windaus, Bloor and others who have modified and improved the various procedures

With this renewed interest in cholesterol there developed as a natural aftermath the desire to express the abnormal blood cholesterol findings in terms of liver function The search for liver function tests, however, has so far met with pessimistic results And it may well be in disease of an organ such as the liver, with its many diverse activities, embracing metabolic, excretory, detoxifying and synthesizing functions, that only partial functional disturbances will occur In such an event, it is possible that several activities will show aberrations, while others will remain intact The great size of the organ, the margin of safety, and the marked compensatory and regenerative powers of the liver have mitigated against the finding of a single liver function test to evaluate the functional and pathologic state of the organ In previous publica-

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From the Medical Services and the Laboratories of the Mount Sinai Hospital

Read before the American Society of Clinical Pathologists, June 7, 1935,  
Atlantic City, N J

1 Flint, A, Jr Am J M Sc 44 305, 1862

tions we have avoided the term "liver function test" in evaluating the findings concerning the blood cholesterol and its ester in hepatic and biliary diseases and have merely attempted to correlate the findings with pathologic and clinical observations

It is beyond the scope of this communication to consider all the experimental and clinical evidence that has been accumulated on the subject of the relationship of the liver to cholesterol metabolism. Excellent reviews that thoroughly cover this subject have been written by Hueck, Buiger, Thannhauser, Gardner and Gainsborough, Adler, Schonheimer, Leupold, Bloor, Van Slyke and Peters, Sobotka and others

This paper deals with the study of the behavior of the plasma cholesterol and its ester in more than 500 cases of hepatic and biliary tract disease observed in the wards of the Mount Sinai Hospital, New York. In the group with hepatic damage, only those cases are presented in which there existed either clinical unanimity of diagnosis or verification of the diagnosis by observations at necropsy. Among the cases of obstructive and nonobstructive diseases of the biliary tract we have included only those in which the diagnosis was verified by operation and autopsy

The colorimetric method of Bloor and Knudson<sup>2</sup> was employed. Repeated determinations are easily carried out on small amounts of blood, and the method provides a sufficient degree of accuracy for clinical purposes. Using this method, we consider the normal variation of cholesterol in 100 cc of blood plasma to be between 150 and 220 mg, of which 50 to 70 per cent is in the form of cholesterol ester. Because of the physiologic variations in the hourly blood cholesterol levels shown by McEachern and Gilmour,<sup>3</sup> McClure and Huntsinger,<sup>4</sup> Gardner<sup>5</sup> and Bruger and Somach,<sup>6</sup> we have always obtained samples of blood before breakfast

Since the previous publications by one of us (E. Z. E.)<sup>7</sup> we have been better able to evaluate the blood cholesterol partition in hepatic and biliary diseases and have usually found definite correlation between the findings in the blood and the clinicopathologic state of the liver

2 Bloor, W. R. *J. Biol. Chem.* **24**: 227, 1916. Bloor, W. R., and Knudson, A. *ibid.* **27**: 107, 1916.

3 McEachern, J. M., and Gilmour, C. R. *Canad. M. A. J.* **26**: 30, 1932.

4 McClure, C. W., and Huntsinger, M. E. *J. Biol. Chem.* **76**: 1, 1928.

5 Gardner, J. A. *Brit. M. J.* **2**: 392, 1932.

6 Bruger, M., and Somach, I. *J. Biol. Chem.* **97**: 23, 1932.

7 Epstein, E. Z. (a) Cholesterol Partition of Blood Plasma in Parenchymatous Diseases of Liver, *Arch. Int. Med.* **47**: 82 (Jan.) 1931, (b) Cholesterol of Blood Plasma in Hepatic and Biliary Diseases, *ibid.* **50**: 203 (Aug.) 1932.

## OBSTRUCTIVE JAUNDICE

This group consists of 105 unselected instances of obstruction of the biliary duct system by neoplasms, calculi, strictures, glands, etc. All cases were verified either by operation or by autopsy (A summary of the findings appears in table 1)

In 82 cases (78 per cent) hypercholesterolemia was present—more than 300 mg of total cholesterol in 100 cc of blood plasma. The highest total was 1,500 mg in 100 cc found in case 1. Although in all the cases there was definite obstruction to the outflow of bile, there was no absolute parallelism between the degree of hyperbilirubinemia and hypercholesterolemia. In case 53, with an icterus index of 160, there was a total cholesterol of 395 mg, whereas in case 1, with an icterus index of 100, there was a total cholesterol of 1,500 mg in 100 cc of blood plasma.

Although no diagnostic significance is to be attached to it, the cases of obstruction of the biliary passages by carcinoma (1 to 52) showed a more marked hypercholesterolemia than the cases due to calculi, strictures, etc (53 to 105).

The duration of jaundice before admission of the patient to the hospital varied from one day to several months, and the degree of hypercholesterolemia showed no relationship to the length of time until the symptoms of terminal cholemia or infection developed, after which a terminal lowering of the cholesterol figures usually occurred. In many cases of obstruction due to carcinoma the obstruction lasted for months without evidence of hepatic damage, superimposed infection or cholemia. In the cases of obstruction due to stones, the duration of the jaundice affected the hypercholesterolemia more frequently. It seemed as though complications were more common in the cases in which obstruction was caused by calculi.

The relief of the obstruction, either by removal of the calculi or by producing circuitous channels, such as cholecystogastrostomy, biliary fistula, etc., resulted in a lowering of the hypercholesterolemia.

In 23 instances of obstruction (22 per cent of our cases) hypercholesterolemia was not found, 8 were due to carcinomas and 15 to calculi in the biliary tract system. An explanation for the absence of hypercholesterolemia in these 23 cases cannot be given. However, in cases 15, 17, 21, 42, 74, 75, 96 and 103 there was only one determination of the blood cholesterol, and it is conceivable that the later level might have been higher. In cases 15, 98, 99 and 105 the degree of obstruction was slight, and the level of the blood cholesterol was correspondingly not high. In cases 21, 42, 86, 89, 90, 97 and 105 the patients were

TABLE 1—*Obstructive Jaundice*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg per 100 Cc of Plasma			Comment
						Total	Ester	Free	
1	65	M	4 wks	5/ 3/33 5/15/33	100 75	1,500 940	935 625	565 315	Carcinoma of papilla of Vater Cholecystogastrostomy, 5/9/33 Necropsy
2	46	F	5 days	3/14/33 3/16/33	80 85	500 625	390 375	110 250	Operation infiltrating carcinoma of cystic and common bile duct
3	38	M	3 wks	12/26/30 1/ 8/31 1/16/31 2/ 9/31 2/28/31	65 30 16 30 75	750 625 280 695 750	470 375 150 375 375	280 240 130 320 375	Operation carcinoma of papilla of Vater Waning and waning of icterus
4	60	M	2 wks	4/14/31	60	625	415	210	Necropsy carcinoma of gall bladder and cystic duct invading and stenosing common bile duct
5	66	F	2 mos	7/29/33 8/ 1/33	120 120	530 355	375 185	155 170	Operation carcinoma of papilla of Vater
6	43	M	3 wks	9/18/31	60	470	240	230	Necropsy carcinoma of head of pancreas
7	38	F		5/17/32 5/18/32	110 90	290 310	170 185	120 125	Necropsy carcinoma of head of pancreas
8	61	M	8 days	11/ 4/31	60	310	155	155	Operation carcinoma of head of pancreas
9	70	M	7 wks	6/ 6/33	120	570	375	195	Necropsy carcinoma of ampulla of Vater with complete obstruction of common bile duct
10	64	M	4 days	10/29/31	50	415	270	145	Operation carcinoma of head of pancreas
11	56	F	5 mos	9/ 7/32	95	325	170	155	Operation carcinoma of head of pancreas
12	45	M	5 wks	3/24/33	90	500	250	250	Operation carcinoma of head of pancreas
13	43	M	2 wks	4/ 2/31 6/22/31	42 120	375 340	90 190	285 150	Operation carcinoma of head of pancreas
14	72	F	2 days	4/11/33	110	315	210	105	Operation carcinoma of gall-bladder with complete obstruction of common bile duct
15	63	F	3 days	4/15/32	40	240	160	80	Operation carcinoma of cystic duct with metastases to glands of porta hepatitis
16	41	M	6 wks 2d adm	6/16/32 6/22/32 8/17/32	105 105 110	240 210 535	160 105 145	80 105 390	Necropsy carcinoma of head of pancreas Jaundice had persisted since May 1932
17	54	M	3 wks	9/11/33	65	280	130	150	Operation carcinoma of head of pancreas
18	52	M	3 wks	8/19/33 9/ 4/33 9/ 7/33 9/12/33	90 105 65 50	290 220 250 215	185 160 145 120	105 60 105 95	Cholecystogastrostomy 8/25/33, carcinoma of head of pancreas
19	70	M	1½ wks	3/19/32	100	225	115	110	Necropsy carcinoma of head of pancreas
20	59	M	3 wks	3/13/31 4/ 3/31	200 250	415 270	235 50	180 220	Clinically patient went into cholemia Necropsy 4/4/31 carcinoma of head of pancreas, stenosing common bile duct with cholangietic abscesses of liver Note drop of total and ester cholesterol with increasing jaundice day before death
21	32	F	1 mo	3/26/30	100	225	105	120	Operation, 3/24/30 carcinoma of head of pancreas Cholemia Patient died 4 days after operation
22	40	F	4 wks	11/ 5/30	80	470	270	200	Operation carcinoma of head of pancreas
23	43	M	3 wks	1/29/31 2/ 5/31 3/ 6/31	35 25	355 535 340	150 290 270	205 245 70	Operation carcinoma of gall bladder with metastases to porta hepatitis

TABLE 1—*Obstructive Jaundice—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg per 100 Cc of Plasma			Comment
						Total	Ester	Free	
24	57	F	10 days	1/14/31 1/29/31	56 55	315 340	105 105	210 235	Operation metastatic carcinoma of liver and of hilar lymph nodes
25	46	M	2 mos	3/11/33	160	280	190	90	Necropsy carcinoma of gall bladder with metastases to hilar lymph nodes
26	55	F	10 wks	5/11/32	125	340	115	225	Necropsy complete obstruction of common duct by calculi, scirrhous carcinoma of extrahepatic bile ducts
27	52	M	9 mos	9/ 3/30	85	535	60	475	Necropsy carcinoma of head of pancreas with stenosis of papilla of Vater Jaundice for 9 months before admission Note low ester
28	55	M	3 wks	2/27/31 3/ 2/31 3/11/31 3/24/31	110 60 48 70	680 935 625 660	470 625 375 430	210 310 250 230	Necropsy occlusion of papilla of Vater by carcinoma
29	72	M	1 wk	6/23/31	30	310	210	100	Obstruction of common bile duct aspiration of liver revealed adenocarcinoma cells
30	45	M	10 days	4/30/32 5/ 3/32	100 140	470 570	310 340	160 230	Operation, September 1923 adenocarcinoma of stomach Increasing icterus before admission
31	65	M	10 days	8/ 9/33 8/19/33	130 35	415 190	200 45	215 145	Cholecystostomy 8/12/33 profuse biliary drainage Patient drowsy, disoriented, cholemic, 8/19/33 Note low ester Necropsy carcinoma of head of pancreas infiltrating common bile duct
32	52	M	14 days	9/ 1/33 9/ 5/33 9/ 9/33	60 80 35	415 290 170	220 95 45	195 195 125	Cholecystogastrostomy, 9/5/33 carcinoma of head of pancreas
33	40	M	1 day	3/ 7/34 4/18/34 4/26/34	8 40 85	250 410	75 135	175 275	Necropsy carcinoma of testis with diffuse metastases in liver and lymph nodes Compression of common hepatic duct by nodes
34	40	F	3 mos	6/ 1/34 6/ 7/34 6/ 9/34	110 90	340 400 155	235 235 45	105 165 110	Cholecystogastrostomy, 6/8/34 carcinoma of head of pancreas Patient died 6/9/34
35	35	M	2 days	1/30/34 2/19/34 2/23/34	35 18 14	375 300 220	210 145 80	165 155 140	Cholecystogastrostomy, 2/13/34, carcinoma of head of pancreas
36	32	M	5 wks	7/21/30 7/28/30 8/ 5/30 8/14/30	150 150	800 680 520 585	90 90 75 35	710 590 445 550	Necropsy adenocarcinoma of rectum, infiltration and occlusion of common bile duct by metastatic hilar nodes Low ester unexplained
37	66	F	2 wks	5/20/30 5/26/30 6/ 4/30	150	750 600 225	235 215 30	515 385 195	Operation, 6/2/30 carcinoma of papilla of Vater Drain age by tube in common bile duct for 12 days
38	53	M	6 wks	11/ 2/32 11/23/32	220 50	325 270	210 215	115 55	Cholecystogastrostomy, 11/8/32 carcinoma of head of pancreas Necropsy confirmed diagnosis
39	65	F	4 days	3/15/34 3/22/34	100	325 240	235 45	90 195	Operation carcinoma of the cystic duct with obstruction of the common bile duct
40	60	M	4 wks	2/23/34 3/ 7/34 3/10/34 3/24/34	105 104 68 30	1,165 535 440 470	750 310 235 340	415 225 205 130	Cholecystogastrostomy, 3/2/34 carcinoma of head of pancreas
41	71	M		2/ 3/32	75	310	180	130	Operation carcinoma of head of pancreas
42	69	F	1 day	6/17/33	44	190	40	150	Necropsy carcinoma of gall bladder with perforation and abscess of liver, biliary peritonitis
43	42	M	2 wks	12/27/34 1/ 3/35	80 180	310 310	260 100	50 210	Operation carcinoma of head of pancreas

TABLE 1—*Obstructive Jaundice—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg per 100 Cc of Plasma			Comment
						Total	Ester	Free	
44	58	F	2 wks	10/30/34 11/ 5/34 11/15/34	130 110 80	450 415 440	330 235 165	120 180 275	Operation, 11/7/34 carcinoma of head of pancreas Cholecystostomy with profuse drainage
45	53	M	6 wks	12/18/33 12/22/33 1/17/34	110 90 35	750 535 240	540 310 65	210 225 175	Cholecystogastrostomy, 1/3/34 carcinoma of head of pancreas
46	54	M	1 day	12/ 5/34 12/12/34 12/17/34	68 120 38	340 420 340	170 210 145	170 210 195	Operation, 12/12/34 carcinoma of common bile duct Cholecystogastrostomy
47	36	M	10 wks	2/17/34	120	375	125	250	Operation scirrhus carcinoma of hepatic bile duct with obstruction
48	56	M	3 days	9/17/34 9/28/34 10/ 8/34	20 40 90	315 260 270	235 120 150	80 140 120	Operation, 10/12/34 carcinoma of head of pancreas
49	64	F	3 wks	10/23/34 10/29/34 11/ 3/34 11/16/34	35 45 80 77	340 325 415 500	105 265 265 375	235 60 150 125	Operation 11/21/34 carcinoma of gallbladder with obstruction of common bile duct
50	55	M		12/14/34	50	375	195	180	Necropsy carcinoma of stomach, metastases to porta hepatis, obstructing common bile duct
51	31	F	2 mos	10/22/34	110	1,170	1,040	130	Operation carcinoma of stomach with metastases obstructing common bile duct
52	58	F	7 days	1/ 8/34 1/15/34 1/22/34 2/ 5/34	110 120 85 80	470 290 235 290	245 110 120 145	225 180 115 145	Operation, 1/12/34 adenocarcinoma of gallbladder with infiltration of common bile duct
53	52	F	5 wks	2/13/31	160	395	210	185	Operation stones in common bile duct and gallbladder
54	58	F	2 wks	11/ 6/32	90	360	200	160	Operation stones in common bile duct
55	52	M	6 days	12/ 1/32	70	310	155	155	Operation stone in common bile duct
56	41	F	9 days	4/10/31	45	625	470	155	Operation large stone completely occluding common bile duct
57	52	F	"few days"	5/ 3/33	105	340	210	130	Operation common bile duct distended with stones
58	48	F		6/ 6/33 6/ 8/33	11 33	440	255	185	Operation common bile duct markedly dilated with large and small stones Note Hypercholesterolemia preceded icterus
59	69	F	12 wks	7/12/33	95	325	180	145	Operation common bile duct dilated with stones
60	65	M	8 days	2/24/33	80	330	250	80	Operation stone in common bile duct
61	57	F	5 wks	3/ 7/33	25	340	165	175	Operation one large and several smaller stones in common bile duct
62	65	F	1 mo	11/30/31	30	310	170	140	Operation common bile duct markedly distended with stones
63	61	M	3 days	4/27/33	35	300	160	140	Operation large stone in common bile duct
64	44	F	2 mos	3/29/33 4/ 7/33 4/17/33	50 50 30	375 290 290	265 150 170	110 140 120	Operation, 4/3/33 stones in common bile duct
65	70	F	Intermittent 9 mos	10/20/33 11/ 1/33	44 20	315 250	190 100	125 150	Operation, 10/28/33 common duct dilated and full of stones Pathologic cholecystogastrostomy found Drain in common bile duct until 11/29/33
66	39	M	1 day	2/12/33	35	340	155	185	Operation common bile duct dilated with stones
67	28	M	6 days	4/23/31	140	375	170	205	Operation common bile duct obstruction by echinococcus cyst
68	38	F		3/17/31 3/24/31 3/29/31	75 65 80	270 360 380	150 200 150	120 160 230	Operation common bile duct obstructed by traumatic stricture

TABLE 1—*Obstructive Jaundice—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg per 100 Cc of Plasma			Comment
						Total	Ester	Free	
69	56	F	4 wks	1/27/33	80	340	200	140	Operation common bile duct dilated by one large and several small stones
70	36	F	1 day	7/22/29	60	365	220	145	Operation stones in common and hepatic bile ducts
71	62	F	3 days	11/11/30	40	535	345	240	Operation very large stone obstructing common bile duct
72	60	M	1 wk	11/10/30	50	535	290	245	Operation stone obstructing common bile duct
73	59	M	10 wks	1/20/31	45	310	205	105	Operation, 1/29/31 large stone in common bile duct Patient went into ehemia Neeropsy, 2/9/31
				2/ 5/31	100	215	80	135	
74	58	F	2 mos	2/ 3/33	30	290	115	175	Operation enormously distended common bile duct filled with calculi and masses of sand
75	29	F	2 days	12/ 3/32	80	190	100	90	Operation stone in retro duodenal portion of common bile duct
76	44	F	2 days	4/30/30	60	250	25	225	Operation, 5/10/30 stone in common bile duct, drainage of common bile duct
				5/26/30	50	245	85	160	
				6/ 6/30		170	45	125	
77	42	M	4 wks	5/22/31	105	340	210	130	Operation, 5/25/31 many stones in common bile duct Free drainage of bile
				6/ 8/31	60	310	110	200	
				6/15/31	30	300	85	215	
78	60	M	3 wks	7/ 1/30	50	220	80	140	Operation large stone in common bile duct
				8/ 4/30		270	135	135	
79	54	M	2 wks	5/21/34	55	340	205	135	Operation obstruction of common bile duct by adhesions due to previous operation
				5/31/34	80	270	105	165	
				6/12/34	55	325	140	185	
80	55	M	3 days	3/26/34	50	250	75	175	Operation common bile duct dilated with stones Drain in common bile duct from 3/27/34 4/2/34 History of repeated attacks of jaundice in past 2 years
				3/29/34	65	215	35	180	
				4/ 4/34	40	210	65	145	
				4/28/34	13	230	115	115	
81	50	F	5 yrs	4/16/34	45	560	290	270	Neeropsy complete stenosis of common bile duct (traumatic at operation 5 years previously), chronic cholangitis and pericholangitis
82	58	M	1 mo	1/17/34	55	375	145	230	Operation, 5/19/34 markedly distended gallbladder, on aspiration foul, infected bile obtained, stones in common bile duct, cholangitis Profuse biliary drainage Instituted Patient entered hospital 3d time with biliary fistula from previous operation Injection of iodized poppyseed oil 40 per cent through drainage tube reveals markedly dilated common duct, narrowed at papilla of Vater
			2 days	(1st adm) 5/ 9/34	35	250	50	200	
				(2d adm) 5/24/34	27	250	Traces	±250	
			3 mos	6/ 2/34	18	235	100	135	
				(3d adm) 8/ 6/34	18	325	250	75	
83	26	F	8 mos	4/21/34	83	415	170	245	Operation, 5/1/34 stricture of common bile duct (due to previous severing 7 months ago following cholecystectomy) Hepatoduodenostomy over a tube performed
			Intermittent	5/ 2/34	85	395	100	295	
				5/ 7/34	28	290	95	195	
84	29	F	3 mos	6/ 5/34	85	415	210	205	Operation, 6/15/34 common bile duct dilated by stones
				6/12/34		355	145	210	
85	54	M	10 mos	5/ 4/31	80	410	180	230	Neeropsy, 11/5/31 common bile duct dilated, chronic cholangitis with biliary cirrhosis
				10/31/31 (2d adm)	100	270	120	150	
86	58	M	7 wks	12/26/31	40	290	105	185	Neeropsy stone in common bile duct, occluding papilla of Vater, obstructive biliary cirrhosis
				1/ 9/31		155	80	75	
				1/16/31	105	130	90	40	

TABLE 1—*Obstructive Jaundice—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg per 100 Cc of Plasma			Comment
						Total	Ester	Free	
87	50	F	1 yr	1/11/32	25	470	310	160	Operation, 2/13/32 common bile duct completely severed (result of previous operation) Tube placed in proximal end of common duct and bile drained to outside
				3/ 1/32		260	120	140	
				3/14/32	18	190	115	75	
88	40	M	7 wks	4/21/34	40	275	130	145	Operation stones in gall bladder and common bile duct
				4/25/34	30	500	125	375	
				5/ 2/34	35	415	155	260	
89	62	M		4/31/32	120	115	Trace	±115	Neeropsy stone in common duct with partial obstruction at ampulla of Vater, acute purulent cholangitis, and cholangiolitis Histologic diagnosis degeneration of liver cells
90	50	F	1 day	10/11/32	30	190	40	150	Neeropsy stones in common mon bile duct, acute chole-dochitis, suppurative cholangitis, abscesses of liver
91	30	F	3 wks	1/13/35	135	310	235	75	Operation, 1/15/35 stones in common bile duct Drained for 16 days
				1/18/35	160	235	80	155	
				1/21/35	110	210	115	95	
				1/24/35	100	150	70	80	
92	38	M	7 wks	2/14/32	120	430	265	165	Operation, 3/7/34 stones in common bile duct
				2/22/32	80	470	310	160	
				12/18/33	15	375	250	125	
				(2d adm)					
				(3d adm)					
93	38	M	10 days	2/26/34	10	355	170	185	Operation, 10/14/33 common bile duct and hepatic ducts enormously dilated with stones
				9/21/33	30	455	250	205	
				10/13/33	30	375	205	170	
94	50	M	9 days	8/ 9/34	26	395	170	225	Operation, 11/2/34 stones in common bile duct
				8/16/34	11	340	210	130	
				11/ 2/34	25	310	135	175	
				(2d adm)					
95	60	F	3 days	5/15/34	14	480	275	205	Operation stones in common bile duct
				5/22/34	10	340	200	140	
96	65	F		11/26/32	45	280	180	100	Operation common bile duct dilated by stones
97	35	F	1 wk	1/17/34	42	270	95	175	Operation, 1/24/34 stone in common bile duct Neeropsy acute cholangitis, subhepatic abscess
				1/26/34	50	250	30	220	
98	40	F	2 mos	2/15/34	12	190	35	155	Operation, 2/27/34 stone in common bile duct Drainage profuse
				2/19/34	22	210	70	140	
				4/ 7/34	4	155	30	125	
99	39	F		4/17/34	28	265	100	165	Operation, 4/20/34 stones in common bile duct, biliary fistula for 5 weeks
				4/19/34	15	235	70	165	
				4/25/34	14	110	Trace	±110	
				5/26/34	9	170	30	140	
100	54	F	2 wks	5/19/34	45	1,340	850	490	Operation, 5/25/34 stone occluding common bile duct
				5/26/34	60	1,070	625	445	
101	49	M	4 mos	2/19/34	48	300	145	155	Operation, 3/6/34 common bile duct dilated with stones Reentered for persistent biliary drainage, icterus and fever Cholangitis
				3/16/34	40	290	200	90	
				4/12/34	60	220	65	155	
				(2d adm)					
				4/23/34	50	265	100	165	
				5/14/34	40	310	135	175	
102	50	F		2/27/34	20	485	300	185	Operation stone in common bile duct
103	41	F	1 day	2/ 1/35	20	200	55	145	Operation, 2/1/35 stones in common bile duct
104	47	F	4 wks	10/23/34	100	290	200	90	Operation, 10/29/34 stones in common bile duct Drainage
				10/26/34		290	185	105	
				11/ 2/34	30	175	95	80	
105	54	F		1/18/35	15	275	145	130	Operations, 1/22/35 stones in common bile duct Neeropsy, 2/4/35 acute cholangitis
				2/ 2/35	17	200	105	95	



observed only after the occurrence of complications such as cholemia, perforation of the gallbladder with abscess of the liver, acute purulent cholangitis and cholangiolitis (a term used to denote infections in the very fine biliary channels) with liver cell degeneration and acute choledochitis

The cholesterol ester of the blood plasma was elevated above 150 mg in 100 cc in 79 of the 105 cases of obstructive jaundice (75 per cent)

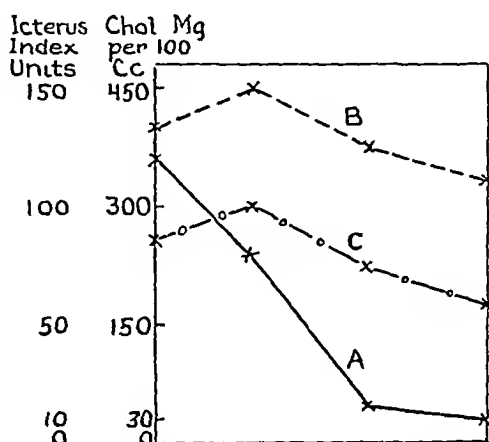


Chart 1—A typical case of obstruction of the common bile duct by stones, with hyperbilirubinemia paralleling hypercholesterolemia (total [B] and ester [C]) With relief of the obstruction and fall of the icterus index (A) there was gradual lowering of the cholesterol level Note the more rapid fall of the icterus index

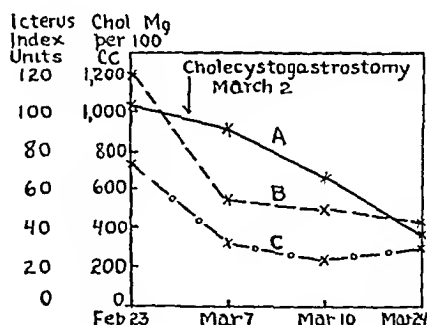


Chart 2—A typical case of jaundice due to obstruction of the common bile duct by carcinoma of the head of the pancreas At the onset there was the usual hyperbilirubinemia with hypercholesterolemia (total [B] and ester [C]) With relief of the obstruction by cholecystogastrostomy there was gradual lessening of the jaundice together with lowering of the cholesterol level A is the icterus index

In 7 of these 79 instances (cases 37, 61, 66, 67, 83, 85 and 94) the elevation of cholesterol ester was not proportional to the increase in the free cholesterol With subsidence of the obstruction and lowering of the bilirubin and total cholesterol of the blood, the cholesterol ester fell proportionately

Of the 26 instances of obstructive jaundice in which the blood cholesterol ester was below 150 mg in 100 cc, the ester remained normal or slightly raised in 18. No explanation can be given for this failure of the cholesterol ester to rise with obstruction of the biliary tract system. In 8 cases the cholesterol ester dropped below normal. A perusal of the records on these 8 cases revealed that complications were present in 5, which would suggest secondary hepatic damage. In case 27, at the time of admission, jaundice has been present for nine

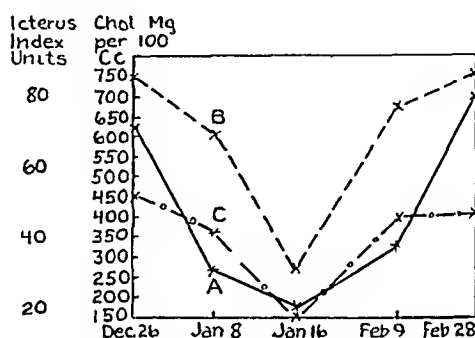


Chart 3—A case of jaundice due to obstruction of the common bile duct by carcinoma of the papilla of Vater. Note the parallelism between the hyperbilirubinemia and the hypercholesterolemia. As the icterus index (A) diminished, the cholesterol (total [B] and ester [C]) also diminished, and as the jaundice increased again, the cholesterol level rose sharply. Waxing and waning of icterus were followed closely by the level of cholesterol.

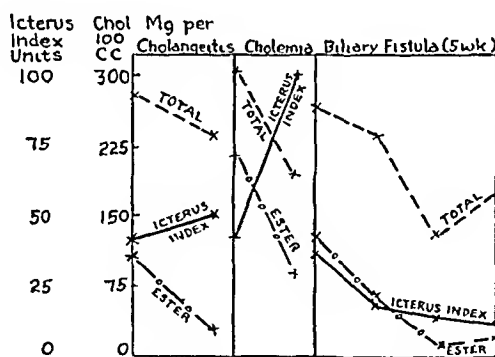


Chart 4—Three cases of obstructive jaundice complicated, respectively, by cholangitis, cholemia and biliary fistula. When cholangitis and cholemia complicated the picture, the total and cholesterol ester diminished as the icterus index rose (owing to the complication of hepatic damage). In the case in which there was a biliary fistula, as the icterus index diminished, the total cholesterol fell, but the cholesterol ester was considerably lowered.

months, in case 42 there was a perforation of the gallbladder with hepatic abscesses, in case 82, at the time of entrance, the cholesterol ester was high, it dropped with the appearance of cholangitis and returned to the former level after drainage of the common bile duct, in case 89 microscopic examination at autopsy revealed acute purulent

cholangitis and cholangiolitis as well as liver cell degeneration, in case 90 there were suppurative cholangitis and hepatic abscesses. In cases 76, 98 and 103 the drop in cholesterol ester was unexplainable.

## COMMENT

The association of hypercholesterolemia and hyperbilirubinemia in obstructive jaundice has been emphasized in the past by many authors: Chauffard, Laroche and Grigaut,<sup>8</sup> Beumer and Burger,<sup>9</sup> Feigl,<sup>10</sup> Bang,<sup>11</sup> Rothschild and Felsen,<sup>12</sup> Stepp,<sup>13</sup> Adler and Lemmel,<sup>14</sup> Gardner and Gainsborough,<sup>15</sup> Epstein,<sup>7</sup> Stroebe,<sup>16</sup> Mjassnikow,<sup>17</sup> Heinlein,<sup>18</sup> and Lehnherr.<sup>19</sup> Exceptions were noted by Stepp when such factors as cachexia and poor resorption of fat supervened over a long time, and by Rothschild and Felsen when high temperatures and infections occurred. Later, Adler, Epstein, Stroebe and others also found that infections in the biliary tract, cholemia, cachexia and damage to the liver subsequent to long-standing stasis were marked by absence of the customary hypercholesterolemia or else by a drop in an existing hypercholesterolemia in a previously uncomplicated case. Cases of obstruction complicated by severe infections usually fail to show hypercholesterolemia.

The hypercholesterolemia occurring in obstructive jaundice had been previously considered to be a retention phenomenon. This was based on the belief that cholesterol was excreted mainly by the liver. Since the work of Sperry,<sup>20</sup> Salomon,<sup>21</sup> Schonheimer,<sup>22</sup> Burger and Winterseel,<sup>23</sup> and Burger and Habs,<sup>24</sup> it is known that the main excretion of

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24 Burger, M., and Habs, H. *Klin Wchnschr* **6** 2221, 1927

cholesterol occurs through the intestinal mucosa. Because of the low concentration of cholesterol in the bile, it would require a complete obstruction of long duration to produce an increase of the total cholesterol from 200 to 400 mg in 100 cc of blood plasma. It is known that within a few days after complete obstruction of the biliary passages the cholesterol of the blood may be doubled or tripled. In the light of these facts the cause of hypercholesterolemia in obstructive jaundice remains as yet unclear.

Burger and Gardner and Gainsborough reported that the hypercholesterolemia associated with obstructive biliary lesions is mainly due to increase in the free cholesterol fraction and that the ester cholesterol is not proportionately raised. They believed that the relatively diminished cholesterol ester of the blood represents diminished absorption. They explained it as the result of faulty absorption of fat, the absence of bile from the intestines also resulting in a reduction in absorption of the cholesterol which exists in the intestines in the form of the ester. However, these authors observed some instances of hypercholesterolemia with high esters in spite of persistent absence of bile from the intestines and failure of the resorption of fat. Stroebe also found that the hypercholesterolemia of obstructive jaundice was mainly in the form of an increase in the free cholesterol with a relative diminution in the ester. However, von Rosztóczy<sup>25</sup> in experimental ligation of the common bile duct in rabbits found both the free and the ester cholesterol to be increased in the blood, and only when the liver was damaged by the stasis did a change in the total cholesterol and the relationship of ester to free cholesterol occur. Likewise, Stern and Suchantke<sup>26</sup> found increased free and ester cholesterol in the blood after ligation of the ductus choledochus in a dog.

Our results contradict the observations of Burger and Gardner and Gainsborough. We have found an elevation of the cholesterol esters of the blood plasma in 75 per cent of our cases of obstruction of the common duct in which little or no bile or urobilin was present in the stool. Conversely the ester of the blood may be low when bile is present in generous amounts in the intestines. In the cases of obstruction in which prolonged drainage or a biliary fistula has been instituted and nearly all the bile diverted from the intestines, the cholesterol ester is lowered considerably in some, but remains normal or elevated in a like number. It may be seen in table 1 that the degree of free and ester hypercholesterolemia does not vary in relationship to the duration of the obstructive jaundice. This has been recently confirmed experi-

<sup>25</sup> von Rosztóczy, E. *Ztschr f d ges exper Med* **68** 690, 1929.

<sup>26</sup> Stern, R., and Suchantke, G. *Arch f exper Path u Pharmacol* **115** 221, 1926.

mentally by Hawkins and Wright,<sup>27</sup> who found that in dogs with biliary fistulas the absence of bile in the intestine with faulty absorption of fat does not cause the development of hypocholesterolemia with dissociation of the ester ratio

#### PARENCHYMATOUS DISEASES OF THE LIVER

In this group, 111 cases of jaundice due to diffuse parenchymatous diseases of the liver are presented (table 2) Among these cases are

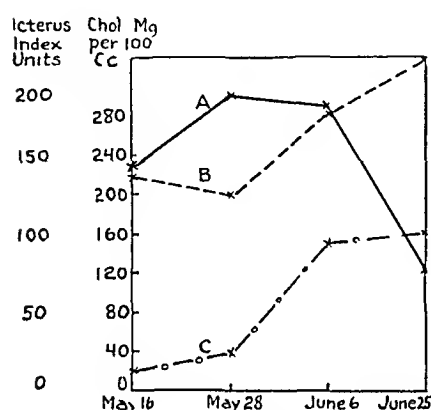


Figure 5

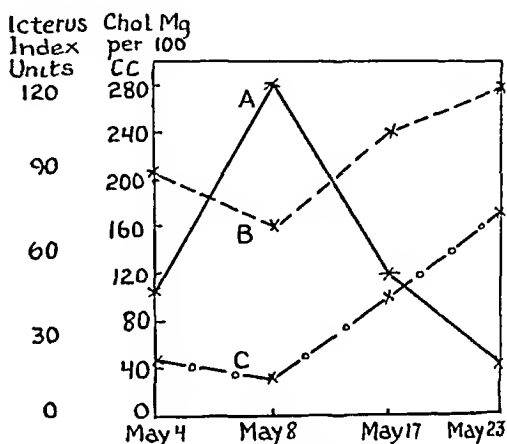


Figure 6

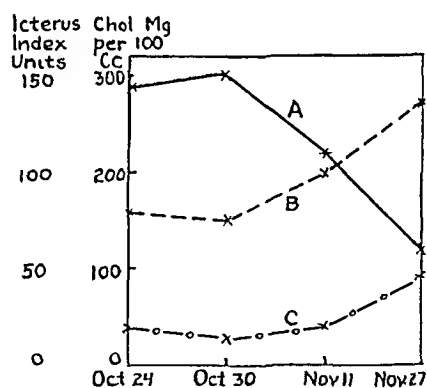


Figure 7

Charts 5, 6 and 7—Typical cases of jaundice, occurring in the course of acute degeneration of the liver. With marked jaundice the cholesterol ester (C) diminished considerably, and with diminution in the icterus index (A) the cholesterol ester rose to normal. The ester fraction closely mirrored the severity of the damage to the liver, being low when the damage was marked and returning to normal with a favorable outcome of the case. B is the total cholesterol.

included instances of hepatic damage following the administration of such drugs as arsphenamine preparations, cinchophen and its derivatives, and in various diseases such as pneumonia and sepsis, and primary dis-

27 Hawkins, W. B., and Wright, A. J. *Exper Med* 59: 427, 1934

eases of the liver such as so-called catarrhal jaundice, toxic hepatitis and hepatosis. Acute, subacute and chronic yellow atrophy and their sequelae, the coarse nodular cirrhoses, are treated under a separate heading.

The parallelism between the bilirubinemia and cholesterolemia observed in cases of obstruction to the common bile duct was not observed in this group of parenchymatous diseases of the liver with jaundice. Although the jaundice was often intense and the icterus index reached 270 in one instance, the total blood cholesterol was above 300 mg in 100 cc of plasma in only 11 of 111 cases of acute degeneration of the liver as compared with 82 of 105 cases of obstructive jaundice with comparable degrees of icterus.

The divergence between the levels of the cholesterol and bilirubin in the blood in acute degeneration of the liver and the parallelism in obstructive jaundice afford valuable aid in the differentiation between the two types of jaundice.

In the remaining 100 cases of acute degeneration of the liver with considerable increase in the bilirubinemia, the total cholesterol of the blood remained below 300 mg in 100 cc. In 24 instances the cholesterol was below 150 mg in 100 cc of blood plasma, in 40 instances, between 150 and 200 mg, and in 36 instances, between 200 and 300 mg. With improvement in the clinical condition, normal cholesterol levels were reached, and during the stage of reparation and regeneration even hypercholesterolemia occurred in some cases.

In 75 cases of acute degeneration of the liver the values of cholesterol ester were found to be lowered at the onset of the illness, when the jaundice was marked and the clinical course at its height. With improvement in the condition of the patient and diminution in the jaundice, the cholesterol ester slowly rose until it reached normal and even supernormal levels. The ester fraction seems to mirror the degree of hepatic damage, tending to remain low in cases of severe hepatic injury. A persistently lowered ester level indicates an unfavorable and serious outcome, whereas a rising level parallels clinical improvement. In severe hepatic degeneration only traces of cholesterol ester may be shown during the early and most intense stage of the disease, whereas in the mild disease often only slight subnormal deviations are observed. A study of the cholesterol ester seems therefore to be of some aid in gaining an insight into both the severity of the disease and the prognosis.

From a perusal of the data on the 111 cases in table 2 it will be seen that 75 followed this simple mathematical formula of severe icterus, normal or even subnormal total cholesterol and diminished cholesterol ester. However, in 36 instances of jaundice in which the clinical picture and course were apparently similar the same results did not

occur Here, the figures for total cholesterol and ester approached normal although the jaundice was intense and the condition of the patient appeared serious in many instances (cases 76-111 in table 2)

The explanation of the normal blood cholesterol partition in these 36 cases of acute degeneration of the liver is difficult In the majority of these cases the disease was mild It is possible that regeneration and reparation were sufficient to offset the damage, which was mild in spite of the intense jaundice Klemperer,<sup>28</sup> in discussing the problem of so-called catarrhal jaundice, said, "clinical and histological studies have shown that hepatic lesions are responsible for many of these cases But similar considerations indicate that another group of identical symptomatology is due to ascending or descending cholangiolitis and not essentially to liver damage" The entire definition of catarrhal jaundice is rather vague, and it is possible that some of our 36 cases fall into the group mentioned by Klemperer as cases of ascending or descending cholangiolitis Moreover, in 10 of these 36 cases of acute

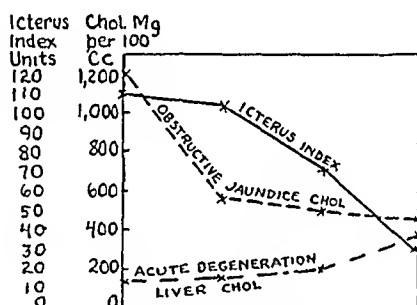


Chart 8—The chart demonstrates the parallelism between the total cholesterol and the icterus index in obstructive jaundice and the divergence between the two in acute degeneration of the liver This difference is of considerable aid in differentiation between the two types of jaundice

hepatic degeneration with normal cholesterol values the condition was either associated with the secondary stage of syphilis or followed arsphenamine therapy Bauer has likewise found that the galactose tolerance test is frequently negative in cases of jaundice in the secondary stage of syphilis or following arsphenamine therapy Six of the 36 cases occurred in children in whom the cholesterol levels were normal

In 4 additional cases of what appeared to be clinically acute hepatic degeneration, the total and ester cholesterol approached the high levels seen in obstructive jaundice, total cholesterol reaching 1,250 mg in one case No explanation could be advanced for this occurrence<sup>29</sup>

<sup>28</sup> Klemperer, P New York State J Med **33** 1309, 1933

<sup>29</sup> This patient suffered from marked alcoholism and after the subsidence of the jaundice had hypercholesterolemia (500 mg in 100 cc of plasma) for several months afterward This case was considered to be one of toxic hepatitis complicating extreme fatty degeneration of the liver

TABLE 2—Jaundice in Parenchymatous Disease of the Liver

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg per 100 Cc of Plasma			Comment
						Total	Ester	Free	
1	19	M	3 wks	11/12/31	150	185	60	125	Vomiting, weakness and painless jaundice 3 weeks, enlarged liver and spleen. Patient improved rapidly
				11/17/31	95	190	135	55	
				11/27/31	75	290	155	135	
2	25	M	7 wks	6/25/31	45	145	40	105	Jaundice 7 weeks, liver below umbilicus, tender, spleen palpable. Patient gradually improved
				6/29/31	35	200	50	150	
				7/ 6/31	40	325	80	245	
				7/20/31	30	310	135	175	
3	38	M	4 days	8/ 5/32	150	195	30	165	Headaches, weakness, chills and painless jaundice 4 days, liver enlarged slightly. Patient improved rapidly
				8/12/32	60	270	170	100	
4	19	M	4 days	12/31/31	150	105	30	75	Miliary tuberculosis of lung and skin, hepatosplenomegaly jaundice, which gradually improved, general condition bad, patient emaciated
				1/18/32	55	220	115	105	
				2/ 5/32	20	120	30	90	
5	32	M	1 day	3/17/32	60	135	Traces	$\pm 135$	Headache, malaise and joint pains 1 week, vomiting 4 days, jaundice 1 day, liver tender, spleen palpable. Patient improved
				3/22/32	90	175	110	65	
				4/ 2/32	30	270	145	125	
6	15	F	2 days	6/10/32	20	220	55	165	Nausea and malaise 6 days, jaundice 2 days, condition considered mild hepatitis
				6/18/32	13	245	135	110	
7	36	F	3 days	4/20/32	120	130	45	85	Generalized aches and pains 2 weeks, jaundice 3 days, positive galactose test. Patient improved in 3 weeks
				4/27/32	115	140	50	90	
				5/ 9/32	30	250	185	65	
8	22	M	9 days	11/16/32	160	220	40	180	Anorexia and malaise 2 weeks jaundice 9 days, liver enlarged, spleen palpable. Patient improved rapidly
				11/22/32	50	300	135	165	
9	28	M	10 days	5/16/31	120	235	Traces	$\pm 235$	Painful, swollen joints with fever for 1 month followed 10 days later by increasing jaundice, liver percussed small, condition considered at first acute yellow atrophy. Patient gradually improved one year later perfectly well
				5/26/31	220	210	40	170	
				6/ 6/31	210	285	160	125	
				6/25/31	75	375	155	220	
10	17	M	1 day	8/10/33	17	200	55	145	Anorexia 2 days, jaundice 1 day, liver enlarged, spleen palpable, soft, mild hepatitis. Patient improving rapidly
				8/18/33	16	200	65	135	
				9/ 1/33	12	300	155	145	
11	38	M	12 days	11/ 3/33	50	200	45	155	Six weeks ago giant urticaria, nausea and diarrhea 3 weeks, jaundice 12 days, liver enlarged. Patient improved rapidly
12	14	M	5 days	3/13/33	27	200	70	130	Nausea and anorexia 1 week, jaundice 5 days, condition considered mild catarrhal jaundice. Patient improved rapidly
				3/16/33	20	220	90	130	
				3/28/33	15	260	110	150	
13	21	F	3 days	8/29/31	30	185	Traces	$\pm 185$	Fever, generalized aches and pains 10 days, nausea, vomiting 8 days, jaundice 3 days, liver and spleen enlarged. Patient improved, 1 year later, well
				9/10/31	12	220	60	160	
14	34	M	6 days	5/10/32	35	165	30	135	Anorexia and nausea 2 weeks, jaundice 6 days, liver enlarged. Patient well and discharged at end of 1 week
15	43	F	1 day	7/11/31	110	195	70	125	Five days of nausea, vomiting, eruption on legs, jaundice 1 day, liver enlarged, spleen palpable, two years later, patient well
				7/22/31	105	235	50	185	
				7/27/31	60	270	140	130	
16	26	F	5 days	6/30/33	35	210	65	145	Chills and fever with painless jaundice 5 days, considered mild attack of toxic hepatitis. Patient improved rapidly



TABLE 2—Jaundice in Parenchymatous Disease of the Liver—Continued

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg per 100 Ce of Plasma			Comment
						Total	Ester	Free	
17	26	M	2 days	10/ 1/31 10/ 5/31 10/ 7/31	110 45 45	170 200 185	Traces 65 25	±170 135 160	Joint pains, anorexia and loss of weight 4 weeks, jaundice 2 days liver enlarged, spleen palpable Patient gradually improved
18	24	M	10 days	9/ 5/30	60	180	40	140	Malaise and painless jaundice 10 days, liver enlarged, acute toxic hepatitis Patient improved December 1930, well
19	26	M	4 days	9/11/33	110	150	Traces	±150	Headache, anorexia, jaundice 4 days, liver and spleen enlarged Patient left hospital against advice Catarrhal Jaundice
20	22	M	9 days	3/14/33 3/18/33	30 45	140 175	55 75	85 100	Nausea, vomiting and painless jaundice 9 days, liver and spleen enlarged Patient improved rapidly
21	28	F	15 days	10/24/33 10/30/33 11/11/33 11/27/33	140 150 110 70	135 150 190 270	35 20 25 80	120 130 165 190	Malaise, anorexia, vomiting and jaundice 15 days, patient very sick and toxic improved slowly
22	23	M	2 days	10/30/33 11/ 1/33 11/ 5/33	80 50 38	190 190 240	50 90 60	140 100 180	Anorexia, nausea and weakness 9 days, jaundice 2 days liver enlarged Patient gradually improved
23	48	F	1 wk	9/26/32	70	200	60	140	Ingestion of atophan for 1 week followed by painless jaundice 1 week later, liver enlarged, toxic hepatitis following atophan Patient improved
24	26	M	1 day	9/10/31 9/22/31	95 25	185 220	Traces	±185 35 185	Headache, fever and anorexia 9 days, jaundice 1 day liver enlarged, spleen palpable Patient improved
25	32	M	6 days	4/ 8/30 4/18/30 5/14/30	70 120 20	150 215 310	Traces	±150 55 190 120	Anorexia belching and diarrhea 10 days, jaundice 6 days, liver enlarged Patient improved
26	52	M	36 hrs	12/16/29 2/10/30	35 12	240 220	55 170	185 50	Jaundice after intravenous hypertonic saline infusions for thrombo angitis obliterans Patient improved after 12 weeks
27	40	M		4/ 2/30 4/ 8/30 4/14/30	75 35 25	120 150 275	Traces	±120 35 135 140	Patient entered hospital for malnutrition After 12 doses of luminal generalized dermatitis developed, followed 13 days later by jaundice, condition considered toxic hepatitis following ingestion of luminal
28	31	F	10 days	5/10/30 5/17/30 5/26/30 6/ 8/30	100 100 100 40	140 155 310	Traces	±140 65 170 140	Following ingestion of large doses of emchophen, jaundice developed, liver and spleen enlarged, condition thought at first to be atrophy of liver Patient very ill, improved slowly
29	39	F	1 wk	7/12/30 7/24/30	70 30	135 190	50 140	85 50	Progressive painless jaundice, anorexia and nausea 1 week subacute hepatitis Patient improved rapidly
30	24	M	2 wks	7/30/30 8/ 4/30	200 30	135 190	Traces	±135 60 130	Nausea vomiting, painless jaundice liver enlarged Patient improved gradually
31	41	M	1 day	12/30/30	140	100	35	65	Jaundice in the course of lobar pneumonia of entire left lung Necropsy degeneration of liver
32	51	M	1 day	10/20/32 10/31/32	40 20	270 200	90 55	180 145	Diarrhea 2 weeks jaundice 1 day liver enlarged and tender, subacute hepatitis Patient improved rapidly
33	19	M	2 days	9/24/32	100	190	70	120	Diarrhea 2 weeks anorexia and nausea 1 week, jaundice 2 days, liver slightly enlarged Patient improved rapidly

TABLE 2—*Jaundice in Parenchymatous Disease of the Liver—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg per 100 Ce of Plasma			Comment
						Total	Ester	Free	
34	47	M	3 days	6/21/31	100	250	100	150	Nausea and vomiting 2 weeks, following medication, jaundice 3 days, liver enlarged Patient improved gradually
				6/29/31	55	310	60	250	
				7/6/31	30	250	145	105	
				7/13/21	38	355	120	235	
35	52	F	5 days	5/17/33	75	235	95	140	Headaches, nausea and anorexia 5 weeks, arthritic pains 2 weeks, jaundice 5 days, liver enlarged, slightly tender Patient improved
				5/25/33	35	235	65	170	
36	52	M	3 days	4/24/33	240	180	100	80	Vomiting 5 days, jaundice 3 days, liver enlarged Patient improved slowly
				5/1/33	120	190	75	115	
				5/10/33	120	155	35	120	
				5/15/33	125	170	75	95	
37	38	F		2/14/34	22	145	50	95	Jaundice developed in the course of pneumonia of left lower lobe, liver enlarged Patient recovered rapidly
				2/19/34	12	260	120	140	
38	29	F		10/7/33	16	160	40	120	Jaundice developed in the course of pneumonia of left upper and left lower lobe Patient improved rapidly
				10/13/33	11	235	125	110	
39	28	F	8 wks	5/4/34	250	165	30	135	Eight weeks painless jaundice with abdominal enlargement 1 week, liver and spleen enlarged, ascites Condition considered at first subacute yellow atrophy Patient gradually improved
				5/8/34	145	175	40	135	
				5/16/34	70	270	115	155	
40	11	M	1 day	1/13/34	40	165	40	125	Jaundice 9 days after drainage of abscess of right foot Condition considered toxic hepatitis Patient improved
41	30	M	2 days	5/4/34	45	210	50	160	Anorexia, nausea, painless jaundice few days, liver percussed small Patient improved gradually
				5/8/34	120	170	40	130	
				5/17/34	38	250	115	135	
				5/23/34	22	300	170	130	
42	45	M	4 wks	3/27/34	48	190	35	155	Alcoholic spree, anorexia and loss of weight, jaundice 4 weeks, liver enlarged Patient improved
				4/7/34	15	250	55	195	
43	34	M	2 days	4/20/34	70	265	80	185	Upper respiratory infection followed by jaundice, liver and spleen enlarged, mild toxic or infectious hepatitis Patient improved
				4/28/34	40	395	235	160	
44	40	M		1/2/35	85	110	40	70	Pneumonia of left lower, right lower, and right middle lobe, followed by jaundice Patient improved gradually
				1/9/35	20	200	70	130	
				1/22/35	12	190	45	145	
45	45	M	1 wk	10/9/34	150	135	55	80	Following alcoholic spree, nausea, vomiting and jaundice 1 week, liver and spleen enlarged Patient improved
				10/12/34	120	140	60	80	
				10/18/34	120	290	170	120	
				10/30/34	40	395	290	105	
46	35	M		8/22/34	38	115	Traces	±115	Two days following appendectomy pneumonia developed in right lower lobe, with jaundice Patient improved
47	33	F	4½ wks	9/22/33	38	225	85	140	Jaundice 4½ weeks, clearing up before admission, liver and spleen enlarged Patient entered toward end of illness
				10/5/33	23	270	135	135	
48	26	M		9/6/34	48	325	220	105	Anorexia, loss of weight and nausea 5 weeks, vomiting 3 weeks, liver enlarged Patient improved
				10/8/34	85	290	40	250	
				10/26/34	24	270	170	100	
49	45	M	4 days	9/17/34	38	200	45	155	Decompensated rheumatic cardiovascular disease with jaundice, enlarged liver Patient improved with digitalis, diuretics and rest
				9/23/34	15	180	115	65	
50	65	M	2 mos	1/27/31	110	140	30	110	Long standing chronic cardiovascular disease, with pulmonary infarcts and jaundice, liver enlarged and tender

TABLE 2—*Jaundice in Parenchymatous Disease of the Liver—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg per 100 Cc of Plasma			Comment
						Total	Ester	Free	
51	42	M	3 wks	4/14/31	22	215	60	155	Rheumatic cardiovalvular disease with decompensation, enlarged, tender liver and jaundice. Patient improved with digitalis and rest
				4/20/31	15	250	135	115	
52	73	F		5/ 5/31	17	190	50	140	Necropsy chronic rheumatic cardiovalvular disease, infarction of lung, chronic passive congestion of liver, jaundice
53	38	F		3/16/31	22	120	30	90	Rheumatic cardiovalvular disease, congestive failure, pulmonary infarction, ascites, enlarged liver, jaundice. Patient improved with digitalis and rest
54	21	M		5/ 5/31	36	155	Traces	±135	Rheumatic cardiovalvular disease, congestive failure pulmonary infarction, enlarged liver, jaundice. Patient improved at first, then became worse and died 6/30/31
55	32	M		4/ 4/31	13	220	50	170	Rheumatic cardiovalvular disease, decompensation, jaundice, enlarged, tender liver. Patient improved with digitalis and rest
				4/18/31		220	110	110	
56	42	M	3 days	6/14/31	110	205	30	175	Chancres 6 weeks ago, lingual sore 4 weeks ago, jaundice 3 days, Wassermann reaction 4 plus, acute toxic degeneration of liver in secondary syphilis
				6/20/31	120	165	Traces	±165	
				6/24/31	80	220	45	175	
				7/ 6/31	33	180	75	105	
57	26	M	16 days	1/14/31	75	145	Traces	±145	Four weeks ago arsphenamine therapy followed by nausea and vomiting, increasing dark urine and painless jaundice 16 days ago, acute hepatic degeneration following arsphenamine
				1/20/31	35	290	170	120	
58	30	M	5 wks	8/26/33	30	170	80	90	Syphilis treated 1 year ago, progressive painless jaundice 5 weeks, lessening in past 2 weeks, liver and spleen palpable. Patient gradually improved
				9/ 1/33	42	250	45	205	
				9/18/33	18	250	145	105	
59	30	M	1 day	10/ 1/31	110	115	40	75	Syphilis, iritis, intravenous antisyphilitic treatment until 3 weeks ago, chills, fever, dark urine, jaundice 1 day, liver enlarged, spleen palpable, toxic hepatic degeneration following arsphenamine. Patient improved
				10/ 5/31	160	195	50	145	
				10/10/31	120	190	55	135	
60	37	F	2½ wks	10/ 1/31	125	130	25	105	Syphilis intravenous injections followed by chills, fever and painless jaundice, liver enlarged, spleen palpable, acute toxic hepatic degeneration following arsphenamine. Patient improved slowly
				10/ 8/31	110	150	30	120	
				10/16/31	65	160	35	125	
				10/22/31	50	210	45	165	
61	29	F	4 days	1/29/33	55	185	85	100	Syphilis, arsphenamine therapy, painless jaundice, malaise and fever 4 days, acute toxic hepatitis following arsphenamine
				2/ 6/33	20	190	125	65	
62	21	M	1 day	2/ 9/31	60	150	30	120	Nausea, vomiting and headache 5 days, jaundice 1 day, mucous patches in mouth, secondary syphilis with mucous patches and syphilitic hepatitis, under bismuth therapy jaundice cleared up
63	65	M	1 day	11/ 7/33	35	160	65	95	Necropsy syphilis, meningococci arthritis and meningitis, bronchopneumonia degeneration of liver with atrophy. Patient had received arsphenamine intravenously before admission
				11/11/33	20	155	25	130	
				11/29/33	13	115	Traces	±115	

TABLE 2—*Jaundice in Parenchymatous Disease of the Liver—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg per 100 Cc of Plasma			Comment
						Total	Ester	Free	
64	20	M	4 days	2/13/30	120	120	40	80	Syphilis, intravenous arsphenamine therapy, followed by jaundice, acute toxic hepatic degeneration following arsphenamine. Patient improved
				2/24/30	40	290	185	105	
65	29	M	4 wks	10/30/30	30	235	70	165	Syphilis following intravenous therapy jaundice developed, liver enlarged condition considered acute hepatic degeneration following arsphenamine. Patient improved
				11/ 6/30	12	210	135	75	
66	43	M		6/12/30	8	115	Traces	$\pm 115$	Syphilis, intravenous injections of arsphenamine followed by fever, vomiting, diffuse dermatitis, no jaundice, patient acutely ill, liver and spleen enlarged
				6/17/30		220	45	175	
				6/30/30	10	200	120	80	
67	51	M	5 days	6/27/33	55	250	80	170	Syphilis treated with bismuth and arsphenamine, nausea and jaundice 5 days, acute hepatic degeneration. Patient improved
68	34	M	7 days	12/23/31	140	235	30	205	Syphilis, treated with intravenous injections, anorexia and drowsiness 2 weeks, jaundice 1 week, liver enlarged and tender, spleen palpable. Patient improved gradually
				12/28/31	80	270	100	170	
				1/ 4/32	35	225	145	80	
				1/11/32	35	320	220	100	
69	34	M	4 wks	2/18/32	270	195	65	130	Syphilis, treated with intravenous injections, malaise, fatigue and jaundice 4 weeks, liver and spleen enlarged. Patient improved, May 1932, well
				2/22/32	200	200	90	110	
				3/ 2/32	80	210	80	130	
70	38	M	13 days	2/ 5/34	150	160	50	110	Syphilis, treated with arsphenamine, fever, anorexia, dizziness and jaundice 13 days, liver enlarged, acute toxic hepatic degeneration following arsphenamine. Patient improved
				2/15/34	45	235	55	180	
				2/19/34	40	260	130	130	
71	50	M	2 days	3/25/32	85	250	85	165	Secondary syphilis with jaundice 2 days, liver enlarged, Wassermann reaction 4 plus, syphilitic hepatitis. Patient improved
72	24	M	1 mo	8/ 7/34	85	105	Traces	$\pm 105$	Syphilis, painless jaundice for past month, liver enlarged. Patient improved
				8/13/34	45	125	30	95	
73	33	M	3 wks	8/ 4/34	85	170	70	100	Syphilis, injections of arsphenamine followed by jaundice. Patient improved slowly
				8/13/34	120	250	130	120	
				8/18/34	110	210	55	155	
74	37	M	12 days	1/19/35	75	160	55	105	Nausea, vomiting and anorexia 1 month, jaundice 12 days, liver and spleen enlarged. Patient improved slowly. Condition considered at first subacute yellow atrophy
				1/26/35	45	160	Traces	$\pm 160$	
				2/12/35	20	155	25	130	
75	30	F	3 days	1/28/35	88	130	30	100	Weakness, nausea, malaise and fever 6 days jaundice 3 days, liver enlarged. Patient improved slowly, on follow up, 4/1/35, well
				2/ 9/35	54	240	70	170	
				2/18/35	40	250	45	205	
76	41	M	2 days	12/30/33	40	250	145	105	Syphilis, treated with arsphenamine, jaundice 2 days, liver enlarged. Patient improved
				1/ 8/34	34	240	135	105	
77	38	M	2 days	3/15/34	50	200	95	105	Syphilis, treated with intravenous injection of arsphenamine jaundice liver enlarged, acute toxic hepatic degeneration after arsphenamine. Patient improved
				3/21/34	70	250	70	180	
				4/20/34	20	375	110	265	

TABLE 2—*Jaundice in Parenchymatous Disease of the Liver—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg per 100 Cc of Plasma			Comment
						Total	Ester	Free	
78	48	M	7 days	5/22/33	100	235	125	110	Syphilis, intravenous arsphenamine therapy, followed by jaundice, liver enlarged Patient improved
79	42	M	6 days	5/15/33	110	260	130	130	Syphilis, intravenous sulfars phenamine therapy, ingestion of einchophen, followed by jaundice, liver enlarged Patient improved
80	43	M		10/ 2/34	38	325	185	140	Syphilis, rheumatic cardiovalvular disease, patient received neoarsphenamine 10 months ago, jaundiced, large liver and spleen, cardiac decompensation, improved with rest
				10/ 8/34	28	290	130	160	
81	39	M	15 days	10/15/32	100	235	105	130	Syphilis, treated with intravenous injections of arsphenamine, jaundice 15 days, liver enlarged Patient improved rapidly
82	38	M	7 days	8/31/33	85	250	135	115	Syphilis, treated with intravenous injections of neoarsphenamine, malaise, nausea and vomiting 5 weeks, jaundice 1 week, liver enlarged Patient improved
				9/18/33	25	210	110	100	
83	23	M	3 days	10/18/34	45	310	170	140	Secondary syphilis with lymphadenopathy, rash and jaundice, Wassermann reaction 4 plus Diagnosis syphilitic hepatitis Patient improved under bismuth therapy
				11/ 7/34	30	340	265	75	
84	45	F	1 day	3/17/31	50	180	80	100	Syphilis, treated with intravenous injections of neoarsphenamine vomiting, chills, fever and jaundice, acute hepatic degeneration following neoarsphenamine
				3/25/31	30	275	125	150	
85	23	F	6 days	7/22/32	120	210	145	65	Syphilis, intravenous injections of arsphenamine, followed by vomiting and jaundice, acute toxic degeneration of liver following arsphenamine Patient improved
86	13	M	1 wk	10/27/34	35	440	250	190	Sore throat, fever and jaundice 1 week Twenty other children in institution afflicted Infectious epidemic catarrhal jaundice Patient improved rapidly
				11/ 5/34	15	290	170	120	
87	45	M	1 wk	9/25/34	175	290	140	150	Patient received intravenous hypertonic saline solution for thromboangitis obliterans, jaundice developed 1 week later, liver and spleen enlarged Patient improved
				10/21/34	150	200	85	115	
				11/ 5/34	110	270	145	125	
				11/17/34	70	320	250	70	
88	57	M	2 wks	2/ 5/34	50	300	180	120	Jaundice following upper respiratory infection liver enlarged Patient improved
				2/13/34	25	270	145	125	
89	51	M	2 wks	4/24/34	55	200	100	100	Malaise, nausea and vomiting 4 weeks, painless jaundice 2 weeks Patient improved
				4/30/34	22	340	235	105	
90	23	M	4 wks	2/16/34	65	200	115	85	Flatulence and pyrosis 5 weeks, painless jaundice 4 weeks, liver enlarged Patient improved
				2/21/34	80	210	120	90	
91	43	M	11 days	10/ 2/34	70	210	110	100	Painless jaundice 11 days diarrhea 1 day Patient improved gradually
				10/11/34	90	230	125	105	
92	21	M		1/18/34	27	235	145	90	Mild attack of grip and sinusitis, followed by jaundice of short duration Patient improved rapidly
93	55	F	7 days	6/16/32	105	270	110	160	Ingestion of 650 grains (44 Gm) of einchophen in 3 months, followed by jaundice Patient gradually improved
				6/21/32	80	250	100	150	

TABLE 2—Jaundice in Parenchymatous Disease of the Liver—Continued

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg per 100 Cc of Plasma			Comment
						Total	Ester	Free	
94	20	M	6 days	5/10/33	100	270	155	115	Pararectal abscess 3 weeks, jaundice 6 days liver enlarged Patient improved rapidly
				5/22/33	45	220	130	90	
95	26	M	4 days	6/ 7/32	80	235	150	85	Malaise, nausea and weakness 2 weeks, jaundice 4 days, liver and spleen enlarged Patient improved rapidly
				6/13/32	30	215	115	100	
96	37	F	10 days	3/14/32	85	290	155	135	Anorexia, pyrosis and nausea 2 weeks, jaundice 10 days, liver enlarged Patient improved slowly
				3/21/32	145	175	80	95	
				4/25/32	36	290	155	135	
97	15	M	7 days	12/ 5/31	40	340	180	160	Anorexia, nausea and epigastric distress 10 days, jaundice 7 days, liver enlarged Patient improved rapidly
				12/10/31	25	290	170	120	
98	14	M	6 days	11/ 2/31	45	310	170	140	Weakness and fatigue 2 weeks, jaundice 6 days, liver enlarged Patient improved rapidly
				11/ 9/31	23	220	115	165	
99	23	F	2 days	10/13/31	85	130	60	70	Nausea and jaundice 2 days, liver and spleen palpable Patient improved
				10/22/31	45	200	80	120	
100	26	M	7 days	5/23/33	85	170	70	100	Progressive painless jaundice 7 days, liver and spleen palpable Patient improved gradually
				6/16/33	50	280	200	80	
101	27	M	3 days	12/24/32	100	190	95	95	Nausea, vomiting, anorexia and jaundice 3 days Patient improved gradually
				1/ 5/33	160	140	90	50	
				1/11/33	75				
102	41	M	4 days	1/12/33	180	170	80	90	Anorexia, pyrosis and jaundice 4 days, liver and spleen enlarged Patient improved slowly
				1/20/33	45	340	130	210	
103	14	F	36 hrs	3/10/33	60	205	100	105	Nausea, vomiting, fever and pain in right upper quadrant of abdomen 9 days jaundice 36 hours Condition probably gastroduodenitis with jaundice Patient improved rapidly
				3/20/33	17	270	170	100	
104	51	M	3 days	6/18/34	60	290	145	145	Arthritic attacks for months patient took heavy doses of drugs, jaundice 3 days, galactose test positive Patient improved
				6/22/34	70	230	95	135	
				7/20/34	55	395	235	160	
105	8	M	6 days	6/15/34	80	300	135	165	Decompensated rheumatic cardiovascular disease Patient improved with rest
				6/19/34	54	290	70	220	
				6/25/34	20	310	135	175	
106	35	F	5 days	12/31/34	90	235	95	140	Infectious mononucleosis, with jaundice developing 5 days before admission Patient improved
				1/ 5/35	56	275	80	195	
				1/10/35	20	250	135	115	
107	27	M	3 days	3/15/34	35	310	155	155	Jaundice following alcoholic spree, liver and spleen enlarged Patient improved
				3/26/34	8	250	145	105	
108	8	M	3 days	5/14/34	35	340	155	185	Anorexia, nausea, vomiting and jaundice 3 days, several children in institution suffered similar attack Patient improved
109	25	M		10/23/34	45	220	125	95	Nausea, vomiting and anorexia 1 week, jaundice on admission Patient improved
				11/ 3/34	20	340	185	155	
110	46	M	2 wks	10/26/34	125	385	310	75	Nausea, vomiting, generalized aches and jaundice 2 weeks Patient improved
				11/12/34	50	310	220	90	
111	13	M		10/15/34	45	250	140	110	Sister and brother had jaundice preceding patient's illness, liver enlarged Patient improved

## COMMENT

As early as 1918, Feigl<sup>30</sup> reported low values of cholesterol ester in a study of the blood lipoids in acute yellow atrophy, but he did not attach any special significance to the observations. It was not until 1926 that a clinical interpretation of the cholesterol partition of the blood in diseases of the liver was reached. Thannhauser and Schaber<sup>31</sup> found not only low values of cholesterol ester in hepatic diseases but also a total disappearance of the ester from the blood in acute yellow atrophy. They called this phenomenon *Estersturz* and believed that it represented a disturbance in the ability of the liver to regulate the level of the blood cholesterol and its esters. Their findings were corroborated by Adler and Lemmel,<sup>32</sup> Wendt,<sup>32</sup> Mancke,<sup>33</sup> Epstein,<sup>7b</sup> Geill,<sup>34</sup> Stioebe,<sup>16</sup> and Mjassnikow.<sup>17</sup>

Adler and Lemmel were able to show in a large series of cases that a fall of the cholesterol ester of the blood plasma occurred in parenchymatous disease of the liver. They demonstrated this by comparing the values of the ester with the results of other tests of hepatic function and concluded that the abnormal cholesterol picture usually parallels disturbances in the other functions of the liver. Most of the other authors cited agreed that the liver plays an important rôle in cholesterol metabolism and that the cholesterol partition reflects disturbances in hepatic function, the exact mechanism of which is not thoroughly understood.

Opposed to this view are the reports of Burger and Habs, Stern and Suchantke, and Gardner and Gainsborough, who expressed the belief that the drop in ester is merely a result of the failure of fat resorption because of the absence of bile from the intestines. In answer to this objection we quote our observations of normal and even markedly increased values of ester in cases of obstructive jaundice in which no bile was present in the intestines, also the markedly lowered values of ester in parenchymatous diseases of the liver in which bile is present in the stools in appreciable amounts. It is therefore safe to assume that the liver must be actively involved in cholesterol metabolism, although the rôle of the fat absorption is an important one.

Animal experimentation has given divergent results. Gebhardt<sup>35</sup> found that there was a marked fall in the total and ester cholesterol in the blood in dogs with Eck fistula and in hepatectomized dogs, whereas

30 Feigl, J. Biochem Ztschr 86 1, 1918

31 Thannhauser, S. J., and Schaber, H. Klin Wchnschr 5 252, 1926

32 Wendt, H. Klin Wchnschr 8 1215, 1929

33 Mancke, R. Deutsches Arch f klin Med 170 358, 1931

34 Geill, T. Hospitaltid 74 1094, 1931

35 Gebhardt, F. Verhandl d deutsch Gesellsch f inn Med 43 215, 1931

Enderlen, Thannhauser and Jenke<sup>36</sup> reported increased values under similar conditions. Moreover, Mann<sup>37</sup> found no significant changes in the blood cholesterol before and at various periods after removal of the liver. Recently work has been done by Hawkins and Wright<sup>27</sup> on the fluctuations of the blood plasma cholesterol due to injury of the liver and obstruction of the bile duct in dogs. They have shown that hypocholesterolemia with dissociation of the normal ratio of esterified to total cholesterol is related to chronic injury of the liver caused by chloroform, and that hypercholesterolemia eventually developed after prolonged biliary obstruction. They also found in dogs with biliary fistulas that the absence of bile in the intestine with faulty fat absorption does not cause the development of hypocholesterolemia with dissociation of the ester ratio. We have had opportunity to make similar observations in dogs, using both chloroform and carbon tetrachloride as hepatic poisons.

We have observed in our series that the total cholesterol of the blood in jaundice due to parenchymatous disease of the liver does not parallel the hyperbilirubinemia. This divergence stands in bold relief to the association of hypercholesterolemia and hyperbilirubinemia seen in most instances of obstruction of the biliary passages. Usually the cholesterol level in cases of hepatic damage is normal or even subnormal, although in a number of cases a slight rise is observed. This increase never reaches that of the cholesterol in cases of obstructive jaundice. Moreover, those cases of parenchymatous disease of the liver in which the initial cholesterol figures are high usually have a favorable termination in spite of the severe degree of jaundice and apparently serious clinical outlook.

The study of the cholesterol esters has given interesting results. In the more severe cases of hepatic damage the cholesterol ester is initially lowered or is present in minute amounts only and remains low when the outcome is fatal. It rises slowly to reach normal proportions when gradual improvement occurs in the course of the disease. In the less severe instances the reduction in the ester at the beginning is not marked, and soon a gradual rise to normal occurs. In some cases the cholesterol levels do not vary from the normal. These may be cases in which the damage is mild or in which the process is in the reparative stage. A few of these cases of jaundice may represent what Klemperer ascribed to ascending or descending cholangiolitis rather than to hepatic damage. A hypercholesterolemia, both total and ester, at times reaching fairly high levels, was found in many instances with regeneration and healing

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36 Enderlen, E., Thannhauser, S. J., and Jenke, M. *Arch. f. exper. Path. u. Pharmacol.* **120** 16, 1927.

37 Mann, F. *Modified Physiologic Processes Following Total Removal of Liver*, *J. A. M. A.* **85** 1472 (Nov. 7) 1925.



The hypercholesterolemia may last for one month after complete recovery

The cholesterol ester seems thus to afford a useful measure of the degree of hepatic damage, falling to low levels with severe degeneration and rising to normal or even above normal with improvement. It has helped materially as an aid in prognosis. Patients with an apparently hopeless clinical outlook and rising ester levels have improved and, conversely, those with apparently mild disease and steadily falling ester levels have gone on to yellow atrophy of the liver and death.

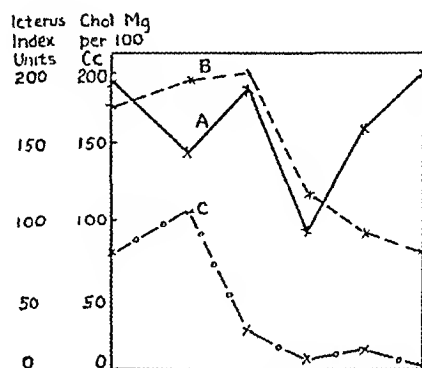


Chart 9—A typical case of acute yellow atrophy, with total cholesterol (B) and ester (C) gradually falling with increasing severity of the disease. The ester was present only in traces toward the end. A is the icterus index.

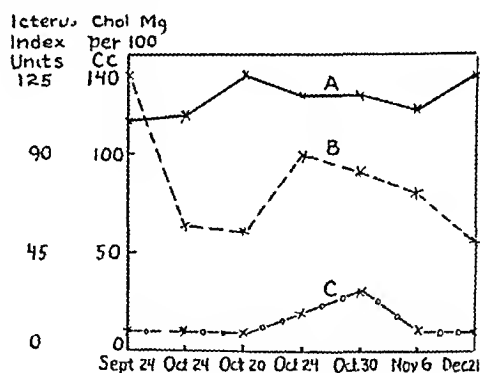


Chart 10—A case of yellow atrophy in the subacute form. The total cholesterol (B) and ester (C) remained low throughout the course of the disease. The ester, on repeated determinations, was present only in traces. A is the icterus index.

#### ATROPHY OF THE LIVER

The significance of the cholesterol ester of the blood in acute hepatic damage as an index of the degree of damage and of the prognosis is best visualized in so-called atrophy of the liver. In table 3 are presented 13 cases of acute, subacute or chronic yellow atrophy with coarse nodular cirrhosis which came to postmortem investigation. Of these, the condition was acute in 5, subacute in 5 and chronic, with nodular cirrhosis, in 3.

The outstanding feature in all the cases was the marked fall of the cholesterol ester, which remained very low throughout the entire fatal course. A steadily dropping ester or the absence of cholesterol ester from the blood in a case of jaundice is of serious import, even when the clinical condition of the patient seems satisfactory.

TABLE 3—*Yellow Atrophy of the Liver*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg per 100 Cc of Plasma		
						Total	Ester	Free
1	41	M	3 days	1/27/33	110	180	20	160
				1/30/33		120	Trace	±120
2	37	F	3 wks	10/16/30	100	175	65	110
				10/27/30	140	105	Trace	±105
3	59	M	1 wk	1/14/31	150	100	Trace	±100
				1/18/31		50	Trace	± 50
4	8	F	2½ wks	10/30/31	185	185	80	105
				11/ 4/31	135	195	95	100
				11/14/31	190	200	30	170
				11/23/31	230	140		
				12/14/31	90	135		
				12/21/31	150	70		
				1/ 4/32	90	115	Trace	±115
				2/15/32	180	100	20	80
				3/ 4/32		80	Trace	± 80
				10/ 9/33	200	210	125	85
				10/13/33	270	170	20	150
5	57	F	1 wk	10/16/33		200	30	170
				10/25/33	250	140	25	115
				10/30/33	235	125	Trace	±125
				5/23/31	200	140	Trace	±140
				5/26/31		100	Trace	±100
6	26	M	4 wks	6/24/30	150	130	Trace	±130
				4/13/31	120	60	Trace	± 60
7	52	F	2 wks	4/17/31	160	70	Trace	± 70
				4/23/31	120	65	0	65
8	12	F	20 mos	5/19/31	110	Trace	0	Trace
				5/26/31		80	0	80
				6/11/31	95	150	55	95
				7/ 6/31	90	110	Trace	±110
9	16	F	1 mo	3/17/31	75	120	40	80
				3/23/31	70	90	35	55
				3/31/31		100	Trace	±100
				4/ 7/31	75	85	0	85
				4/16/31	35	90	0	90
10	35	F	9 wks	2/13/35	75	150	30	120
				2/15/35	75	155	Trace	±155
				2/16/35		115	Trace	±115
11	54	M	5 days	1/25/35	150	190	40	150
				1/28/35	140	165	Trace	±165
				1/29/35		200	20	180
12	28	M	4 days	9/24/31	100	140	Trace	±140
				10/14/31	100	65	Trace	± 65
				10/20/31	125	60	Trace	± 60
				10/24/31		100	20	80
				10/30/31		105	30	75
				11/ 6/31	110	90	Trace	± 90
				12/21/31	125	65	Trace	± 65

The total cholesterol of the blood showed the same relationship to the hyperbilirubinemia as in catarrhal or toxic jaundice, only to an exaggerated degree—namely, lowered total cholesterol in spite of considerable hyperbilirubinemia, the icteric index in one case reaching 270. The total cholesterol values were the lowest we have observed, at times being so low that they could not be measured by the method employed.

## ATROPHIC CIRRHOSIS OF THE LIVER

Thirty cases of atrophic cirrhosis of the liver (Laennec) were studied, of which 17 were examined at necropsy and one at operation. The others were considered typical instances of Laennec's cirrhosis, and in each several of the following observations were recorded: considerable imbibition of alcohol over many years, hematemesis, melena, enlargement and induration of the liver, palpable spleen, evidence of collateral cutaneous circulation, and ascites with repeated paracenteses.

In any study of atrophic cirrhosis of the liver one must recognize at which stage of the disease the patient is seen. These stages represent, respectively, the result of portal obstruction, a superimposed hepatitis in the course of the cirrhosis, or terminal failure of the liver.

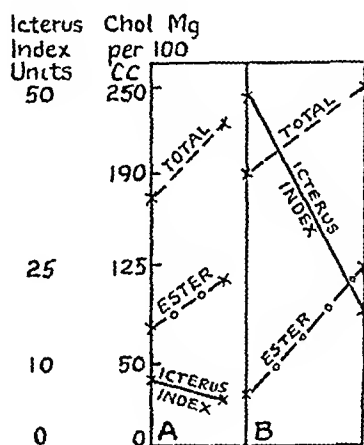


Chart 11—Two typical cases of atrophic cirrhosis of the liver. In *A*, in which portal obstruction was present without jaundice, the cholesterol partition was normal. In *B*, in which there was jaundice due to a superimposed hepatitis, the cholesterol ester was low. With improvement and diminution of the jaundice, the ester gradually rose to normal.

expressed in cholemia. Jaundice in the course of atrophic cirrhosis of the liver is uncommon and, when present, is usually slight. Unless an unrelated obstruction to the biliary passages is present, icterus is usually indicative of a complicating hepatic degeneration.

There were 13 cases of atrophic cirrhosis of the liver in which no jaundice occurred and in which the consequences of the portal obstruction predominated. The blood cholesterol partition was approximately normal with a slight occasional diminution of the cholesterol ester. In 3 cases (21, 22, 27) the postmortem examination revealed, in addition to atrophic portal cirrhosis, a primary carcinoma of the liver. Here the cholesterol figures do not conform with those for the other cirrhoses, perhaps because of the complicating carcinoma.

The remaining 14 cases of atrophic cirrhosis of the liver presented jaundice due either to a superimposed intercurrent degeneration of the

TABLE 4—*Atrophic Cirrhosis of the Liver*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg per 100 Cc of Plasma			Comment
						Total	Ester	Free	
1	66	F		2/26/31	11	205	100	105	Neeropsy atrophic portal cirrhosis
2	64	M		12/22/31	4	225	140	85	Neeropsy atrophic portal cirrhosis
3	60	M		9/22/32	15	220	145	75	Chronic alcoholism, ascites, paracentesis abdominis — 7,000 cc, liver hard and irregular, urine — urobilin
4	46	M	1 wk	1/15/32	20	215	110	105	Neeropsy atrophic portal cirrhosis
5	60	M		1/ 2/35	12	215	50	165	Ascites, collateral circulation paracentesis abdominis, liver enlarged to umbilicus, spleen palpable 3 fingerbreadths, urine, urobilin, Takata Ara reaction strongly positive
				1/18/35	9	200	65	135	
6	53	M		12/11/34	22	270	45	125	Recurrent ascites, multiple paracenteses
				12/18/34		300	100	200	
				12/21/34	28	290	195	95	
				12/26/34		340	165	175	
7	54	M		4/19/34	6	160	95	65	Neeropsy atrophic portal cirrhosis
8	42	M		7/ 5/34	8	535	160	375	Neeropsy atrophic portal cirrhosis
9	39	M		4/29/30		190	90	100	Chronic alcoholism, ascites, esophageal varices
				5/10/30	10	160	50	110	
10	61	F		3/ 8/30	8	210	70	140	Periodic excessive alcoholism, enlarged hard liver, 4 finger breadths below costal margin
11	64	M		1/17/30	22	155	40	115	Neeropsy atrophic portal cirrhosis with adenomas
12	40	F	6 wks	2/ 5/30		195	100	95	Chronic alcoholism, jaundice occurred after alcoholic debauch 6 weeks before admission, liver and spleen enlarged, urine, urobilin
				2/13/30	25	210	95	115	
13	33	M		8/ 7/30	7	130	70	60	Operation cirrhosis of liver Splenectomy
14	62	M		9/21/34	20	190	55	135	Persistent ascites for 5 months prior to admission Paracentesis abdominis performed 5 times Urine — urobilin
				10/ 5/34	20	150	40	110	
15	63	F		9/18/30	16	150	65	85	Neeropsy atrophic portal cirrhosis
16	38	F		10/26/32	9	170	70	100	Recurrent ascites, paracentesis abdominis performed 6 times — 11,000 cc of clear fluid removed during last tap, collateral circulation, urine — urobilin
				11/30/32	6	220	120	100	
17	45	M		3/25/31	12	250	60	190	Neeropsy atrophic portal cirrhosis
				4/11/31	10	270	110	160	
18	48	M		1/29/31	45	120	45	75	Collateral circulation, recurrent ascites with paracentesis abdominis, large spleen, urine — urobilin
19	33	M	3 wks	2/29/32	120	235	65	170	Neeropsy atrophic portal cirrhosis
				3/ 5/32	70	180	50	130	
20	42	F	10 days	2/15/32	140	120	35	85	Neeropsy portal cirrhosis with areas of hepatic degeneration
21	61	M	1 mo	8/28/31	50	290	120	170	Neeropsy atrophic portal cirrhosis, primary carcinoma of liver
				9/ 4/31	37	265	50	215	
				9/15/31	100	310	90	220	
22	61	M	6 days	12/ 6/32	150	210	55	155	Neeropsy atrophic portal cirrhosis, primary carcinoma of liver
23	36	F	2 mos	9/ 8/31	40	185	35	150	Neeropsy atrophic portal cirrhosis

TABLE 4—*Atrophic Cirrhosis of the Liver—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg per 100 Cc of Plasma			Comment
						Total	Ester	Free	
24	59	M	2 wks	2/ 2/32	36	140	40	100	Increasing ascites 3 weeks, icterus 2 weeks prior to admission, cholemia at time of death, urine — urobilin
25	52	M		2/23/33		60	Tr	±60	Necropsy atrophic portal cirrhosis, focal areas of acute degeneration of liver
				3/13/33	27	100	Tr	±100	
				3/16/33	50	55	Tr	±55	
26	49	M	8 mos	9/15/33	23	105	Tr	±105	Recurrent ascites, icterus 8 months prior to admission, paracenteses abdominis 18 times, cholemia at time of death, urine — urobilin
27	62	M		12/ 3/32	35	420	270	150	Necropsy atrophic portal cirrhosis, primary carcinoma of liver
28	46	M	6½ mos	2/19/31	45	310	170	140	Necropsy atrophic portal cirrhosis
29	60	F	2 mos	1/ 2/34	35	250	195	55	Necropsy atrophic portal cirrhosis with adenomas
				2/ 9/34	40	230	30	200	
				2/20/34	65	165	30	135	
				3/29/34	38	190	80	110	
30	38	M		4/ 9/34	50	170	55	115	Chronic alcoholism, ascites, paracentesis abdominis — 19,000 cc, urine — urobilin
				1/ 9/33	7	150	40	110	

liver or to cholemia in the terminal stage of cirrhosis. In this group of Laennec's cirrhosis with jaundice we observed that the cholesterol partition behaved as in the primary hepatic degenerations. The total cholesterol was subnormal and the cholesterol ester considerably lowered or even entirely absent. The cholesterol ester rose to approximately normal values as clinical improvement occurred (table 4).

The functions of the liver tend to remain normal in the type of hepatic disease exemplified by atrophic portal cirrhosis in which the evolution is slow, the distribution is periportal and regeneration is present. The deviations are present when superimposed hepatitis or terminal cholemia occurs. The total and ester cholesterol showed practically no variations from normal in the cases in which jaundice was absent and in which the mechanical obstruction to the portal circulation produced the outstanding symptoms. When jaundice supervened, the cholesterol partition was similar to that seen in acute degeneration of the liver. The normal blood cholesterol picture in nonjaundiced patients with atrophic portal cirrhosis agrees with previous reports of Adler and Lemmel and of Epstein.

#### NONOBSTRUCTIVE DISEASE OF THE BILIARY TRACT

A group of 30 unselected cases of acute or chronic cholecystitis and cholelithiasis without obstruction in which operation was performed are presented in table 5. Contrary to accepted belief, the cholesterol of the blood plasma was not regularly elevated. In only 8 cases did the total cholesterol reach 300 mg in 100 cc of plasma. The cholesterol

was below 200 mg in 7 instances, and in the remaining ones it was between 200 and 300 mg

The cholesterol ester retained its normal relationship to the total cholesterol in 18 instances. In other instances there was no absolute rise or fall, but the relative proportion remained low. Rothschild and Rosenthal,<sup>38</sup> Campbell,<sup>39</sup> Adler and Lemmel<sup>14</sup> and others also found very little change in the blood cholesterol picture in uncomplicated non-obstructive disease of the biliary tract. Recently Colp, Doubilet and

TABLE 5—*Nonobstructive Disease of Biliary Tract*

Case	Age	Sex	Icterus Index	Cholesterol, Mg per 100 Cc of Plasma		
				Total	Ester	Free
1	24	F	8	250	120	130
2	31	F	7	230	115	115
3	30	M	13	235	115	120
4	45	F	8	325	170	155
5	38	F	30	250	175	75
6	45	F	8	235	95	140
7	46	F	6	360	250	110
8	30	F	13	200	55	145
9	50	F	16	270	85	185
10	49	F	16	240	60	180
11	39	F	8	530	265	265
12	45	F	12	280	110	170
13	56	F	12	325	180	145
14	50	F	10	165	70	95
15	43	F	8	290	70	220
16	39	F	9	575	150	425
17	66	F	6	125	60	65
18	42	F	5	135	65	70
19	34	F	10	350	280	70
20	31	F	8	235	110	125
21	35	F	5	180	125	55
22	31	F	8	135	105	30
23	27	F	6	280	110	170
24	38	F	5	270	150	120
25	32	F	10	300	155	145
26	37	F	5	225	145	80
27	19	F	6	230	125	105
28	53	F	35	175	45	130
				160	85	75
29	45	F	6	340	120	220
30	42	F	5	175	90	85

Gerber<sup>40</sup> were able to study the pathologic changes of the liver in non-obstructive disease of the biliary tract by means of the punch biopsy at operation. Their studies confirm the previous beliefs that little or no damage to the liver occurs in nonobstructive disease of the biliary tract.

#### SUMMARY

We have been purposely careful to avoid the term "liver function test" and have considered the significance of the variations in the plasma cholesterol and ester in diseases of the liver and biliary passages. There are numerous instances of elevated or depressed levels of the blood cholesterol in other diseases, which cannot be considered an expression of a disturbance of hepatic or biliary function. Low levels of total and

38 Rothschild, M. A., and Rosenthal, N. *Am J M Sc* **152** 394, 1916

39 Campbell, J. *Quart J Med* **18**:123, 1924

40 Colp, R., Doubilet, H., and Gerber, I. E. *Ann Surg* **102** 202, 1935

ester cholesterol are observed in some cases of severe infection—such as bacterial endocarditis, cystopyelonephritis, necrotizing infections and pyelophlebitis. With the subsidence of the infection the values for cholesterol again approach normal. Likewise in ulcerative colitis, sprue, severe diarrheas, pernicious anemia, severe secondary anemias and exophthalmic goiter the blood cholesterol partition may be disturbed.

However, the determination of the blood cholesterol and ester has enabled us to improve our accuracy in the diagnosis and prognosis of hepatic and biliary diseases. In obstructive jaundice hypercholesterolemia is usually encountered, affecting both the free and the ester fractions, which parallels the degree of hyperbilirubinemia. With the relief of the obstruction and the lessening of the jaundice, the cholesterol gradually returns to normal. In some instances—long-standing biliary stasis, superimposed infections of the biliary passages, cachexia and other complications—the cholesterol level may not rise above normal.

In jaundice occurring in acute degeneration of the liver blood cholesterol does not rise with the bilirubin, but usually remains normal or subnormal. This divergence between the degrees of blood cholesterol and blood bilirubin in parenchymatous diseases of the liver contrasts sharply with the parallelism between the hyperbilirubinemia and hypercholesterolemia in obstructive jaundice and usually affords a means of differentiation between the two types of jaundice.

The cholesterol ester is usually lowered in acute degeneration of the liver and mirrors the severity of the damage. In rapidly fatal cases the ester is low or even absent throughout the course of the disease. In the cases in which the disease is less severe the initial low values of ester gradually rise to normal with improvement, and in the cases in which the disease is mild the initial levels are only moderately depressed.

In atrophic cirrhosis of the liver (Laennec) the blood cholesterol partition remains normal except when jaundice supervenes in the course of an intercurrent acute hepatic degeneration or terminal cholemia. In these instances the blood cholesterol partition behaves as in the primary degenerations of the liver.

In cholecystitis and cholelithiasis with no obstruction to the biliary outflow the blood cholesterol levels are normal or insignificantly elevated.

In using the cholesterol partition as an aid in the diagnosis and prognosis of diseases of the liver and biliary tract repeated determinations during the course of the illness give an indication of the trend and are therefore of much more value than a single determination. In evaluating the significance of a single determination of the cholesterol partition, erroneous conclusions can usually be avoided, just as with the Wassermann test, if the result is considered in the light of the clinical sequence of events and if allowances are made for the stages of the disease and the possible existence of infections and of extrahepatic diseases which may also influence the cholesterol level of the blood.

# ACTIONS OF DIURETIC DRUGS AND CHANGES IN METABOLITES IN EDEMATOUS PATIENTS

A B STOCKTON, M D

SAN FRANCISCO

In previous papers I have discussed the concurrent changes in the output of urine and in the blood and urinary metabolites of animals and edematous patients treated with diuretic drugs<sup>1</sup> The following drugs produced increases in the output of urine and in the chloride content of the blood and urine sodium bismuth tartrate, theophylline, merbaphen and salyrgan Bismuth caused the same effects in normal and chloride-saturated rabbits but much less pronounced changes in those deprived of chloride In edematous patients the increase in the amount of urinary urea and of uric acid after the administration of bismuth paralleled the diuresis, and the concentration of these metabolites, the dilution of the urine The hemoglobin, sugar, urea and uric acid contents of the blood showed no changes, or only negligible ones, after the administration of bismuth

The effects on the chloride content during diuresis due to digitalis differed This drug reduced the chloride content of the blood and at the same time increased the chloride content of the urine The effects of spontaneous diuresis without the use of drugs were identical with those of diuresis due to digitalis These various results suggested differences in the seat and mechanism of the diuretic actions That is, the purine and the metallodiuretic drugs appeared to mediate the diuretic effects through a direct action on the tissues, in general, while digitalis acted indirectly by way of a circulatory improvement, that is, the purine and the metallodiuretic drugs seemed to act by virtue of the mobilization of salt, while digitalis and also the spontaneous removal of water did not As the data on theophylline, merbaphen and salyrgan were incomplete, the work was continued with special attention to early

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Supported in part by a grant from the Rockefeller Fluid Research Fund of the School of Medicine, Stanford University

1 Stockton, A B Proc Soc Exper Biol & Med **27** 721, 1930, Arch internat de pharmacodyn et de therap **41** 52 1931, Bismuth Diuresis and the Blood and Urinary Changes Under Clinical Conditions, Arch Int Med **50** 142 (July) 1932, Diuretic Effects and Changes in Blood and Urinary Metabolites After Digitalis in Normal and in Edematous Persons, *ibid* **50** 480 (Sept) 1932



changes in the amount of chlorides in the blood and urine. For if it could be shown that increase in the chloride content of the blood preceded increase in the output of urine and in the chloride content of the urine this would be evidence of the mobilization of chlorides from the tissues, in support of the so-called theory of tissue diuresis. Such evidence is offered in this report, which presents the completed data on these diuretic drugs.

### METHODS

Seventeen edematous patients were studied. Fourteen had edema due to cardiac decompensation, and three had portal cirrhosis with ascites and pitting edema of the legs. The patients were divided into three groups. Six received theophylline, six merbaphen and five salyrgan. Each group contained one patient with portal cirrhosis.

All the patients were kept at absolute rest in bed for the duration of the observations. They were given diets low in salt (2 Gm daily) and a constant daily intake of 1,200 cc of fluids. Specimens of urine for analysis were collected at intervals of from fifteen minutes to four hours during the first twenty-four hours and then for variable periods as long as the diuretic action lasted. Specimens of blood were obtained during the control periods at four hour intervals and after the administration of drugs at the same time the specimens of urine were collected.

The control periods varied from patient to patient, but in every case they continued until the intake of fluid, the output of urine and the chloride contents of the blood and urine remained nearly constant for three days.

Theophylline was given orally in capsules immediately after breakfast in total doses ranging between 0.6 and 1.5 Gm. Merbaphen and salyrgan were administered intravenously, the total doses ranging between 0.5 and 2 cc.

The chloride content of the blood was estimated by the method of Austin and Van Slyke<sup>2</sup> and that of the urine by the Seelman-Volhard method<sup>3</sup>. The results are presented in charts 1 to 3 as average percentage changes from the control periods.

### EFFECTS OF VARIOUS DRUGS

*Theophylline*—After the administration of theophylline the onset of diuresis occurred in four hours and continued for about thirty-five hours. Diuresis was at its peak in twenty-two hours. The concentration of chloride in the urine reached a maximum in six hours and again in twenty-three hours. The lowest concentration occurred during the peak of diuresis. The minute output of sodium chloride paralleled almost exactly the curve of diuresis. The chloride content of the blood was at first depressed, it had returned to normal at the end of fourteen hours, and it then reached a maximum in eighteen hours, just preceding the maximum diuresis. At the end of twenty-seven hours, it fell to normal, as the output of urine returned toward normal.

*Merbaphen*—Diuresis (chart 2) began two hours after the administration of merbaphen reached its maximum in five and thirteen hours and persisted in large volume for about sixteen hours. Following this marked diuresis the output of urine remained somewhat above that of the control period for about fourteen hours. The total duration of diuresis was about thirty hours. The concentration

2 Austin, J. H., and Van Slyke, D. D. *J. Biol. Chem.* **41** 345, 1920.

3 Seelman, J. J. *J. Lab. & Clin. Med.* **1** 444, 1916.

of chloride in the urine was increased moderately from the beginning of diuresis and was sustained with some fluctuations during the marked diuresis of the first sixteen hours. The highest concentration occurred during the time of maximum diuresis at the end of thirteen hours. The minute output of urinary chloride closely paralleled the diuresis. The chloride content of the blood began to increase

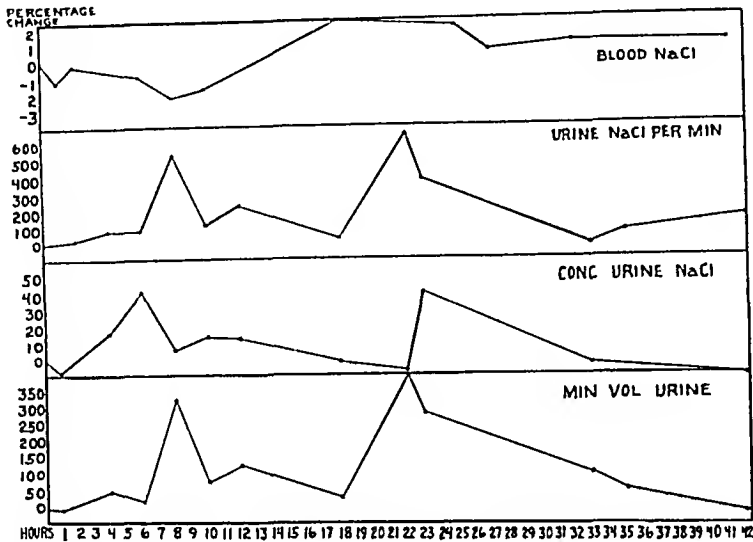


Chart 1—Average percentage of change in the output of urine and in the chloride content of the blood and urine of patients receiving theophylline

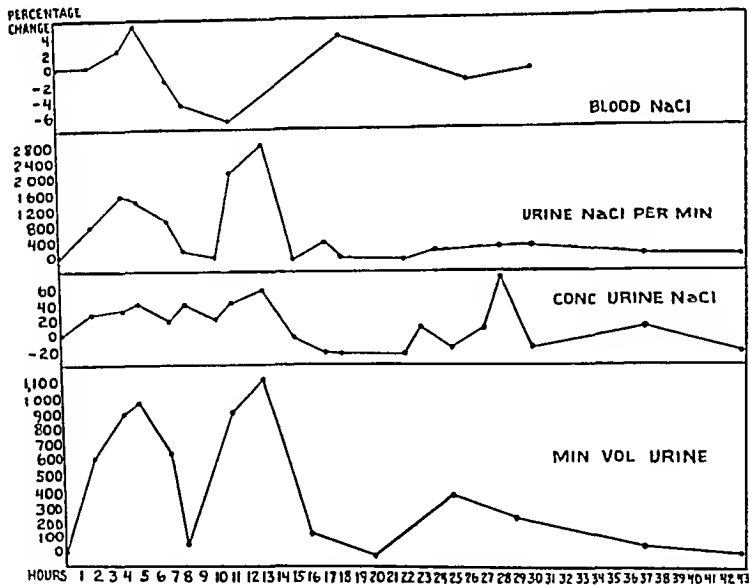


Chart 2—Average percentage of change in the output of urine and in the chloride content of the blood and urine of patients receiving merbaphen

two hours after the administration of the drug. It reached a maximum in five hours, when diuresis was at its height, and then fell, being below the control level at the end of eleven hours. At the end of eighteen hours a second marked elevation occurred, which lasted for about three hours, with somewhat delayed increases in the output of urine and the chloride content of the urine.

*Salyrgan*—Diuresis due to salyrgan (chart 3) began at the end of one hour, reached a maximum in five hours and had returned almost to the control level after twenty hours. The chloride contents of the blood and urine increased in the same way as after the administration of merbaphen, but the amplitude of the increases was greater. The maximum increase in the chloride content of the blood occurred three hours before the maximum increase in diuresis, thus suggesting that diuresis depended on the mobilization of chloride from the tissues. On the whole, salyrgan appeared to be somewhat more effective than merbaphen, but qualitatively it acted the same.

*Comment*—Rearrangement of the patients into groups according to the order of administration of the diuretic drug, *i e.*, before or after the previous administration of a diuretic drug, demonstrated only

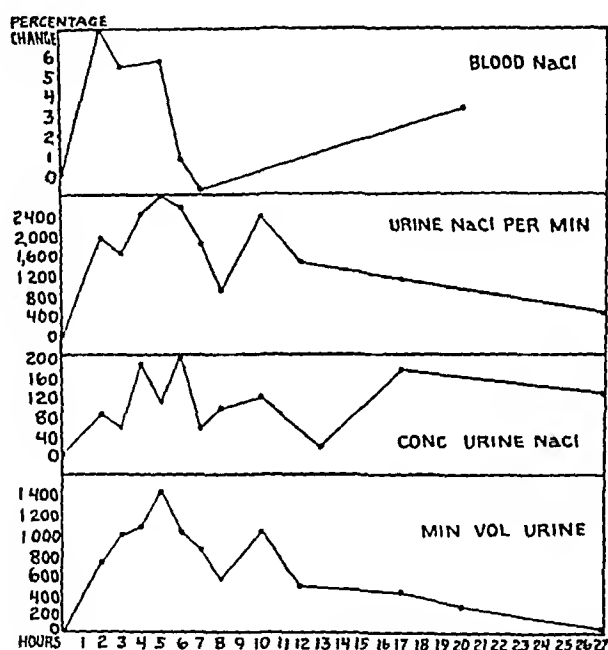


Chart 3—Average percentage of change in the output of urine and in the chloride content of the blood and urine of patients receiving salyrgan

that the average diuretic response was greater after the administration of the first diuretic drug, regardless of the kind. That is to say, the diuretic response to salyrgan was greatest when the drug was used first, and the response was less when it was given after another diuretic drug or when a previous dose of salyrgan had been administered. In making these comparisons, ample time for recovery was always permitted between the giving of diuretic drugs to a patient, the output of urine being allowed to return to the control level and remain there for a minimum of forty-eight hours before another diuretic drug was given. Therefore, the decrease in the response must have been due to the decrease in the quantity of edema fluid in the patient. Any patient who was refractory to one diuretic drug was usually refractory to all

## VARIOUS ADJUVANTS WITH DIURETIC DRUGS

The increased response to diuretic drugs following the oral administration of ammonium nitrate, ammonium chloride, calcium chloride,<sup>4</sup> magnesium sulfate, sodium sulfate,<sup>5</sup> potassium chloride,<sup>6</sup> decholin sodium,<sup>7</sup> urea, hydrochloric acid<sup>8</sup> and other substances has been described by many investigators. It has been claimed that any substance which increases the acidity of urine will increase diuresis. Some investigators have claimed that the diuresis is increased by compounds which contain the chlorine ion in the absence of sodium, such as ammonium chloride, calcium chloride, potassium chloride and hydrochloric acid.

Of the patients studied six were given ammonium chloride in doses of 2.6 Gm daily, two were given 5 Gm of potassium chloride daily and two were placed on a salt-free diet. The group receiving ammonium chloride showed an average increase of 162 per cent (with a range of from +44.8 to -12 per cent) in diuresis. The concentration of chloride in the urine was increased 112 per cent (with a range of from +22.7 to 0 per cent). The daily output of chloride in the urine also was increased to 426 per cent (with a range of from +90 to +6 per cent). The chloride content of the blood remained practically unchanged, showing an increase of only 0.2 per cent at the time of the increase in diuresis.

Two patients receiving potassium chloride also showed an increase in the output of urine as long as the salt was given, i. e., 78.1 per cent above the control level. The daily output of chloride increased 37.3 per cent, but the concentration in the urine fell 10.9 per cent. The chloride content of the blood increased 2.7 per cent, which was not significant, although the increase occurred at the time of the increase in diuresis.

Two patients placed on a salt-free diet also showed a permanent increase in the output of urine. During the first ten days this increase averaged 77.2 per cent, and during the second ten day period, 56.1 per cent. The daily output of chloride fell 1.8 per cent, and the concentration of chloride decreased 58.2 per cent. The chloride content of the blood showed a small decline, of 2.4 per cent.

It is apparent from the results described that increases in diuresis followed the administration of the chlorine ion when it was not combined with sodium. Restricted intake of sodium and of chlorine likewise resulted in diuresis. Torbert and Cheney<sup>9</sup> were able to produce in

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4 Misumi, K. J. Biochem. 5:417, 1925. Keith, N. M. Am. J. Physiol. 68:80, 1924.

5 Bloch, E. Ztschr. f. klin. Med. 106:733, 1927.

6 Barker, M. H. Edema as Influenced by a Low Ratio of Sodium to Potassium Intake, J. A. M. A. 98:2193 (June 18) 1932.

7 Brä, H. Wien. klin. Wchnschr. 41:1080, 1928.

8 Herrmann, G., Schwab, E. H., Alvarez, J. A., and Cate, M. E. Proc. Soc. Exper. Biol. & Med. 30:1375, 1933.

9 Torbert, H. C., and Cheney, G. Reduction in Colloidal Osmotic Pressure of Blood Serum After Salt Ingestion, J. A. M. A. 106:683 (Feb. 29) 1936.

normal subjects a frank pitting edema of the extremities by administering large quantities of sodium chloride and water. Wiley and his co-workers noted the retention of fluids after the administration of sodium bicarbonate. Loeb,<sup>10</sup> Lashmet,<sup>11</sup> Barker<sup>12</sup> and many others have shown the relation of the retention of sodium chloride to the edema occurring in Bright's disease by use of the salt-free diet. Therefore, the sodium ion appears to play an important part in the retention of fluid of edema and ascites. Further evidence of its importance is provided by the following results, which indicate storage of sodium chloride in edema and ascitic fluid of edematous patients.

*Comparative Clinical Effects of Diuretic Drugs\**

	Theo phylline	Merbaphen	Salyrgan	Digitalis	Sodium Bismuth Tartrate
Number of patients	10	7	15	7	21
Dose, Gm or cc	1.30	1.30	1.3	1.4	2.0
Daily output of urine in control period, cc	600.00	601.00	742.0	600.0	512.0
Maximum excretion, percentage change	247.00	330.00	1,081.0	263.0	120.0
Total excretion, percentage change	200.00	285.00	685.0	107.0	187.0
Duration of diuresis, days	1.52	0.82	1.3	4.0	4.2
Concentration of chloride in urine, per centage change	+11.2	+26.2	+76.4	-20.3	-11.0
Maximum chloride content of urine, per centage change	+262	+320	+500	+187	+60
Total chloride content of urine, percent age change	+211	+320	+488	+91	+54
Maximum chloride content of blood, per- centage change	+1.56	+0.6	+6.6	-11.5	+1.2
Total chloride content of blood, percent age change	+0.23	+1.0	+3.8	-10.2	+0.6

\* The maximum percentage change was obtained by averaging the greatest changes observed during diuresis, the total percentage change in the fluid or the chloride content actually removed indicates changes during the entire period of diuresis as compared with the output for an equal control period.

STORAGE OF SODIUM CHLORIDE IN ASCITIC AND EDEMA FLUID

From five of the patients with edema collections of edema fluid were made by means of Southey tubes. Pleural fluid was obtained from two patients with cardiac decompensation and anasarca. Ascitic fluid was obtained after abdominal paracentesis from one patient with cardiac decompensation and from eight patients.

10 Loeb, R. F., and others. *J. Clin. Investigation* **11** 621, 1932.

11 Lashmet, F. H. The Treatment of Nephritic Edema by Acid, *J. A. M. A.* **97** 918 (Sept. 26) 1931.

12 Barker, M. H., and O'Hare, J. P. The Use of Salyrgan in Edema, *J. A. M. A.* **91** 2060 (Dec. 29) 1928. Barker, M. H., and Kirk, E. J. Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, *Arch. Int. Med.* **45** 319 (March) 1930. Barker<sup>6</sup>.

with portal cirrhosis and ascites. The amount of chloride in these fluids was compared in each case with the concentrations of chloride in the blood and urine. In all but two patients the average concentration of chloride in the edema fluid exceeded that of the blood, and in six patients the chloride content of the edema fluid was even higher than the chloride concentration in the urine. The average sodium chloride content of the blood was 418 mg per hundred cubic centimeters (with a range from 385 to 469 mg), while the average concentration in the edema fluid was 618 mg (with a range of from 357 to 1,200 mg) and in the urine 671 mg (with a range of from 360 to 890 mg).

#### COMMENT

In order to facilitate discussion and comparison, important numerical data which I have obtained from this and previous studies of the diuretic drugs are summarized in the accompanying table. The drugs are arranged as follows, in ascending order of effectiveness for removing water from the body: bismuth, digitalis, theophylline, merbaphen and salyrgan. Digitalis and bismuth produce a more prolonged diuresis, which is never so dramatic as the sudden outpouring of urine following the administration of a mercurial diuretic. However, there is often a marked diminution in diuresis after the administration of mercurial diuretics which is not observed after the administration of digitalis and bismuth. The total output of sodium chloride in the urine closely parallels the output of urine and is likewise least after the administration of digitalis and greatest after the administration of salyrgan. Digitalis has no direct effect on the kidney and does not act as a diuretic in patients without congestive heart-failure and edema<sup>13</sup>. Any renal vasoconstriction due to this drug when given in therapeutic doses is overcome by an increase in the local blood flow, which determines the diuretic effects. Theophylline, merbaphen and salyrgan increase the output of urine even in a normal person. Theophylline often produces so much gastric irritation that it cannot be tolerated by the patient. No symptoms of mercurial poisoning were observed after the administration of merbaphen and salyrgan to the patients in the present series. One patient received two 2 cc injections of salyrgan weekly for two years without symptoms of mercurial intoxication.

After the administration of theophylline, merbaphen and salyrgan there is an increase in the chloride content of the blood and a concurrent increase in the concentration of chloride in the urine. Similar results have been observed after the use of theophylline by Curtis<sup>14</sup> and

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13 Stockton, A. B. *Am Heart J* 9 248, 1933

14 Curtis, G. M. *The Action of the Specific Diuretics*, *J A M A* 93 2016 (Dec 28) 1929

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13 Stockton, A. B. *Am Heart J* 9:248, 1933.

14 Curtis, G. M. *The Action of the Specific Diuretics*, J. A. M. A. 93:2016 (Dec. 28) 1929.



Moller,<sup>15</sup> after the use of merbaphen by Lyons<sup>16</sup> and after the administration of salyrgan by Bedford,<sup>17</sup> Crawford and McIntosh,<sup>18</sup> Hatzieganu, Gavrilă and Borbil,<sup>19</sup> Nothmann,<sup>20</sup> Hansen, Fosdick and Dragstedt<sup>21</sup> and others. The increase in the chloride content of the blood is in most cases the first to appear, followed in a short time by an increase in the excretion of chloride in the urine. This can be interpreted only as a prior mobilization of chloride from the tissues and suggests some direct tissue action for these diuretic drugs. A similar conclusion was reached by Melville and Stehle<sup>22</sup> and by Nonnenbruch,<sup>23</sup> who observed the same phenomena. Spontaneous diuresis and diuresis produced by digitalis are characterized by a marked decrease in the concentration of chloride in the blood and also by a decrease in the concentration of chloride in the urine. In spite of the decreased concentration of the chloride, however, the daily output of chloride is increased because of the large amounts of fluid excreted. This type of diuresis suggests a simple washing-out effect on free chloride of the tissues which occurs so rapidly that the tissues are unable to maintain the original chloride level of the blood. Consequently, the chloride content falls.

The chlorine ion is notably concerned in the phenomenon of diuresis. According to Herrmann,<sup>24</sup> Melville and Stehle<sup>25</sup> and Frandsen and Moller,<sup>26</sup> an initially low chloride content of the blood forecasts a poor diuretic response to the xanthine diuretic drugs. The sodium ion itself exerts an antidiuretic action, which can be demonstrated easily by the administration of large amounts of sodium chloride. This results in oliguria and an accumulation of fluid in edematous patients, and even the development of frank edema of the ankles in normal persons. Other chlorides such as potassium chloride, ammonium chloride and hydro-

15 Moller, K. O. *Arch f exper Path u Pharmacol* **126** 143, 1927

16 Lyons, R. M. *Clin North America* **12** 1341, 1929

17 Bedford, D. E. *Proc Roy Soc Med* **24** 429, 1931

18 Crawford, J. H., and McIntosh, J. F. *J Clin Investigation* **1** 333, 1925

19 Hatzieganu, I., Gavrilă, I., and Borbil. *Compt rend Soc de biol* **99** 1813, 1928

20 Nothmann, M. *Arch f exper Path u Pharmacol* **172** 402, 1932

21 Hansen, H. L., Fosdick, L. S., and Dragstedt, C. A. *J Pharmacol & Exper Therap* **41** 325, 1931

22 Melville, K. I., and Stehle, R. L. *Arch f exper Path u Pharmacol* **123** 175, 1927

23 Nonnenbruch, W. *Munchen med Wchnschr* **68** 1282, 1921

24 Herrmann, G., and others. *Diuresis in Patients with Congestive Heart Failure*, *J A M A* **99** 1647 (Nov 12) 1932

25 Melville, K. I., and Stehle, R. L. *J Pharmacol & Exper Therap* **34** 209, 1928

26 Frandsen, J., and Moller, K. O. *Acta med Scandinav* **68** 385, 1928

chloric acid, cause an increase in the output of urine, rich in chloride, which is proof of the antidiuretic effects of the sodium ion

Herrmann and his co-workers<sup>27</sup> and Schmitz and Leiter<sup>28</sup> have employed the Rehberg<sup>29</sup> technic in the study of the mechanism of diuretic action. This procedure alone is not acceptable for the purpose, since it has never been demonstrated that creatinine is a nonthreshold substance. In fact, several workers have reported to the contrary<sup>30</sup> Concurrent increases in the concentration of chloride in the blood and urine and an early prediuretic mobilization of chloride in the blood cannot be explained on the sole basis of decreased tubular reabsorption caused by the diuretic drugs. Moreover, an irritant action of the metallodiuretic drugs on the kidneys could not explain the full effects accompanying diuresis produced by these drugs.

Modern controversies have revolved around the question of the primary seat of action of diuretic drugs, whether it is in the tissues or the kidneys or both. Europeans have generally emphasized the importance of the tissues, while Americans have generally insisted on the importance of the kidneys. Unfortunately, American investigators have not always weighed adequately all the evidence, but when this is done it is difficult to explain satisfactorily the results with some diuretic drugs without giving consideration to a direct action on the tissues. This paper may therefore serve to emphasize the worthiness of this view, certainly, at least, as regards the metallodiuretic drugs. The situation when theophylline is administered appears to be more complicated. My own results with this drug are not as satisfactory as might be desired in support of a tissue action, so that a direct renal action may be the more important factor.

#### CONCLUSIONS

The metallodiuretic drugs, merbaphen, salyrgan and bismuth sodium tartrate probably act directly on the tissues in general and thus produce a mobilization of chloride and water. This explains adequately the observed facts, namely, the increase in the chloride content of the blood preceding the diuresis and the concurrent increase in concentra-

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27 Herrmann, G., Stone, C. T., and Schwab, E. H. Some Studies on the Mechanism of Diuresis in Patients with Congestive Heart Failure, *J. A. M. A.* **98** 2315 (June 25) 1932. Herrmann and others, *J. Lab. & Clin. Med.* **18**:902, 1933. Herrmann and others.<sup>8</sup>

28 Schmitz, H. L., and Leiter, L. *J. Clin. Investigation* **10** 667, 1931. Schmitz, H. L. *ibid.* **11** 1075, 1932.

29 Rehberg, P. B. *Biochem. J.* **20** 447, 1926.

30 Marshall, E. K., Jr. *Am. J. Physiol.* **94** 1, 1930. Jolliffe, N., and Chasis, H. *Proc. Soc. Exper. Biol. & Med.* **30** 586, 1933. Shannon, J. A. *ibid.* **100**: 301, 1932.

tions of chloride in the blood and urine. A direct renal action of these diuretic drugs cannot fully account for these phenomena.

The xanthine diuretic drugs, notably theophylline, apparently exert a similar direct action on the tissues in part at least, but there is a greater variability in the changes in the chloride content and also in diuresis. The diuretic action appears to be partly of direct renal origin.

Spontaneous diuresis and the diuresis of digitalis in decompensated patients are characterized by increases in the urinary output of chloride and simultaneous decreases in the concentration of chlorides in the urine and blood, thus indicating a fundamental difference in the mechanism of diuresis produced by metallodiuretic drugs. Here an improvement of the renal circulation appears to be paramount.

Clinical results in edematous patients indicate the following arrangement of drugs in the ascending order of their diuretic efficiency: bismuth, digitalis, theophylline, merbaphen and salyrgan.

# Progress in Internal Medicine

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## SYPHILIS

A REVIEW OF THE RECENT LITERATURE

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AND

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The present review is similar in every respect to that of a year ago<sup>1</sup> and covers the publications which appeared during the last six months of 1935 and the first six months of 1936. The shorter span of time to be covered has made it possible, in a few instances, to be more detailed, but the limitations of space have again made it necessary to exercise a rigid and sometimes rather arbitrary selection of material. In the field of experimental syphilis, only those articles which are of general interest or which have a direct clinical application have been mentioned, and, aside from one contribution of crucial importance, references to the welter of literature on the serology of syphilis have been almost entirely omitted. The preponderance of the American literature reviewed was not planned, it occurred automatically as a reflection of the heightening of interest in syphilis which is taking place in this country.

### HISTORY OF SYPHILIS

The valuable contributions of Zimmermann,<sup>2</sup> Klauder,<sup>3</sup> Krumbhaar,<sup>4</sup> Beekman<sup>5</sup> and many others do not lend themselves well to review but should be mentioned here. Further studies in paleopathology by Williams<sup>6</sup> and Henschen,<sup>7</sup> however, are of great interest in serving

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From the Syphilis Division of the Medical Clinic, the Johns Hopkins Hospital

1 Moore, J E Syphilis. Review of the Recent Literature, Arch Int Med **56** 1015 (Nov) 1935

2 Zimmermann, E L The Early History of Alopecia Syphilitica, Janus **39** 105 (June-Aug) 1935

3 Klauder, J V Syphilis and the Characters in Ibsen's Dramas, Ann M Hist **8** 236 (May) 1936

4 Krumbhaar, E B Pre-Columbian Peruvian Tibia, Ann M Hist **8** 232 (May) 1936

5 Beekman, F Studies in Aneurysm by William and John Hunter, Ann M Hist **8** 124 (March) 1936

6 Williams, H U The Origin of Syphilis. Evidence from Diseased Bones, Arch Dermat & Syph **33** 783 (May) 1936

7 Henschen, F The Earliest History of Syphilis in Light of More Recent Skeleton Findings, Hygiea **97** 592 (Aug 31) 1935

further to clarify the question of the origin of syphilis in America. To his former reports Williams adds information on three additional groups of bones (from Mexico, Alabama and Illinois) which are unquestionably of precolumbian origin and which are diseased in the manner characteristic of syphilis. Complementary to this, Henschen has reviewed the material of the European museums and reports that, whereas in the anatomic material dated prior to the first portion of the sixteenth century there are to be found no examples of disease of bones like that caused by syphilis, after about 1550 such examples occur in abundance.

#### SPIROCHAETA PALLIDA

The controversy concerning the existence of an invisible form of *Spirochaeta pallida* proceeds with undiminished vigor with, at the moment, the protagonists on the offensive. Nyka,<sup>8</sup> unable to see convincing examples of multiplication of the spiral form of the organism when observing preparations for long periods under the dark field microscope, concludes that reproduction must take place while the organism is in a filamentous stage. With the collaboration of the staffs of the Pasteur and the Alfred Fournier Institute, Levaditi<sup>9</sup> in two long general articles produces the following evidence in favor of an infravisible form of *S. pallida*. 1 *S. pallida* may be found in sections stained by the Dieterlé method (and less easily by dark field examination) of tissues from infected mice, but if heat-killed instead of live organisms are injected into an animal in a similar manner they are not found in sections of remote tissues. This is interpreted as meaning that the organisms in the tissues are developed locally from invisible forms. 2 Tissue from infected animals will produce syphilis in other animals even when no spiral forms of the organism are found in sections or dark field preparations. 3 An initial pause, or pre-spirochete phase, occurs after an animal is inoculated with an emulsion of virulent spirochetes. 4 The difficulties of producing involvement of the central nervous system in experimental animals and the characteristics of human neurosyphilis are adduced to explain the assumption that only the infravisible form of the spirochete may survive in the tissue of the nervous system.

8 Nyka, W. A propos de la multiplication du spirochete syphilitique, *Compt rend Soc de biol* **121** 97, 1936.

9 (a) Levaditi, C., Vaisman, A., Schoen, R., and Manin, Y. Recherches experimentales sur la syphilis (deuxieme memoire) Variations de l'activite pathogene et cycle evolutif du virus syphilitique, *Ann Inst Pasteur* **56** 251 (March) 1936. (b) Levaditi, C., Vaisman, A., and Schoen, R. Recherches experimentales sur la syphilis. Étude pathogénique de la neurosyphilis, *ibid* **56** 481 (May) 1936.

Koch,<sup>10</sup> on the other hand, critically examined the subject and concludes that there is no direct evidence for the existence of an invisible form of *S. pallida* and further that there are no observed phenomena which necessitate for their explanation the hypothecation of an invisible form of the organism. By appropriate experiments he demonstrated that there is no filtrable form of the organism, a point clearly demonstrated by Castellino<sup>11</sup> also. In following a group of animals through the "initial pause" he observed that the argentophilic granules, which Levaditi and his co-workers consider to be another form in the life cycle of the spirochete, could be seen in sections only *after* typical spirochetal forms were present in abundance. He concludes, therefore, that the granules, if related to the spirochetal form at all, represent degeneration products.

*A Spirochete Vaccine*—Levaditi and his collaborators<sup>12</sup> have carried the Truffi strain of *S. pallida* in their laboratory since 1908. Inoculations of human beings in 1914, 1922 and 1935 produced progressively less typical infections, and in 1935 the strain failed entirely to infect a chimpanzee in which typical syphilitic lesions developed when a freshly isolated strain was injected. From this experience they suggest that eventually it may be possible to develop an attenuated organism suitable for use in the vaccination of human beings.

*The Viability of S. Pallida in Excised Tissue*—Pathologists have long wondered to what risks they were exposing themselves in handling tissues from syphilitic patients. Rosahn<sup>12</sup> suggests the answer. Rabbit syphilomas rich in spirochetes were removed and stored at ordinary refrigerator temperature. At intervals varying from twenty-four hours to forty-two days, portions of a syphiloma were ground up and inoculated intratesticularly into rabbits in the usual manner. Infection resulted after the injection of material stored for seven days or less but not after that stored for from fourteen to forty-two days.

#### GENERAL LABORATORY PROCEDURES

*The Staining of S. Pallida*—In a brief communication Krajian<sup>13</sup> describes in duplicatable detail a method for staining *S. pallida* in tissue, which can be carried out from fresh tissue to stained and mounted

10 Koch, F. Ueber Mutation der Spirochaeta pallida, Arch f Dermat u Syph **172** 51, 1935

11 Castellino, P. G. Giornale di dermat e sif **77** 91 (Feb.) 1936

12 Rosahn, P. D. The Infectivity of Treponema Pallidum in Excised Syphilitic Tissue, Am J Hyg **22** 283 (Sept.) 1935

13 Krajian, A. A. A Rapid Method of Staining Spirochaeta Pallida in Single Sections of Tissue, Arch Dermat & Syph **32** 764 (Nov.) 1935

section in an hour and a half. He states that the organisms are easy to find in primary lesions and makes the interesting suggestion that in a central laboratory the diagnosis of early syphilis by means of sections of biopsy material from a suspicious lesion that are stained in this manner may be more reliable than diagnosis by dark field examination of tissue juice which has been transported from a distance. The method has not as yet been sufficiently used to establish its value in detecting the organisms in lesions of late syphilis, which make up the vast majority of necropsy material.

*The Sedimentation Rate in Syphilis*—Gaté and Chevat<sup>14</sup> report studies of the sedimentation rate before and during treatment of 70 patients with various forms of syphilis. Using the method of Cordier, they found the sedimentation rate to be increased by from 8 to 20 per cent in patients with seropositive primary syphilis, and in the group with secondary syphilis it reached as high as 55 per cent. On the institution of treatment the sedimentation rate was observed in some instances to increase, suggesting a provocative response, but in all it soon fell to a level around 15 per cent, there to remain until about the end of the first year of treatment, irrespective of the results of the serologic test for syphilis. There was no uniformity among patients with late or congenital syphilis, but the behavior of the sedimentation rate closely paralleled the clinical course. The authors suggest that from an extension of these observations might be developed a guide for the treatment of early syphilis after seronegativity has been attained.

#### SEROLOGY

Various reports<sup>15</sup> have been given of the meeting of the committee on Evaluation of Serodiagnostic Tests for Syphilis. The following quotation is from an editorial<sup>16</sup> entitled "The American Evaluation of Serodiagnostic Tests for Syphilis from the Clinician's Standpoint."

The report of the meeting of the Committee on Evaluation of Serodiagnostic Tests for Syphilis in the United States, recently held under the auspices of the

14 Gate, J, and Chevat, H. Contribution a l'étude de la sédimentation des Hematies dans la syphilis, *Presse med* **44** 71 (Jan 11) 1936

15 Cumming, H S, Hazen, H H, Sanford, F E, Simpson, Walter M, and Vonderlehr, R A. The Evaluation of Serodiagnostic Tests for Syphilis in the United States. Report of Results, *Ven Dis Inform* **16** 189 (June) 1935. Seneer, F E, Cumming, H S, Hazen, H H, Sanford, A H, Simpson, W M, and Vonderlehr, R A. Evaluation of Serodiagnostic Tests for Syphilis, *South M J* **29** 68 (Jan) 1936. The last mentioned article gives a summary of the report.

16 The American Evaluation of Serodiagnostic Tests for Syphilis from the Clinician's Standpoint, editorial, *Am J Syph, Gonorr & Ven Dis* **20** 207 (March) 1936

United States Public Health Service and the American Society of Clinical Pathologists, is not entirely satisfactory from the standpoint of the clinician. In rating tests as to sensitivity and specificity, doubtful results in both syphilitic and nonsyphilitic patients were excluded from consideration since "there was no general agreement in the proposals offered by the participating serologists for the evaluation of this group of reports." Specificity (as to blood, not spinal fluid, tests—this editorial comment being limited to the results with blood specimens only) was determined by the results in 152 normal nonsyphilitic individuals only, no consideration being given in the widely publicized preliminary reports to the 316 presumably nonsyphilitic patients with diseases and conditions other than syphilis (i e, tuberculosis, neoplasms, jaundice, fevers, pregnancy, menstruation, etc, but excluding the groups of patients with malaria and leprosy). This limitation, corrected in the final report, was deliberate since the 152 normal subjects were considered to be clinically beyond suspicion of infection with syphilis, while it was felt that in spite of every clinical precaution a very small percentage of the 316 presumably nonsyphilitic patients with various conditions might in fact have had syphilis. Finally, the Committee was scrupulously careful to avoid specific recommendations for the adoption of any particular test or group of tests.

Before proceeding to a discussion of these points, it is necessary to point out that the competitive tests were carried out by thirteen serologists, each of whom performed in his own laboratory the test which he himself had devised (exceptions only in the cases of Kurtz, who performed the Kahn presumptive test, and Rein, who performed the Kline exclusion test). In all instances, therefore, the results may be taken to indicate the maximum efficiency of the various tests under the conditions imposed, since the originator of the test may be expected to be more familiar with the major and minor details of his own procedure than technicians in other laboratories. However, the criterion by which any laboratory procedure may be expected to stand or fall is its efficiency in other hands than those of its originator. For this reason, a projected serologic evaluation plan has been properly sponsored by the same agencies responsible for the first and is now under way. In this second project, specimens are being sent to each of several laboratories, as well as to that of the originator of the test, performing, for example, the Kahn or Kline flocculation tests, the Ruediger complement fixation test, etc. The results of this second evaluation will be a much better indicator of the efficiency of the several tests under everyday working conditions in the average serologic laboratory, and the decision as to the relative merits of each properly should be deferred until its conclusion.

The purpose of these comments is, however, to discuss the interpretation of the published results of the original serologic evaluation study from the standpoint of the clinician, whether or not he possesses practical experience in the serologic laboratory. It should be unnecessary to reemphasize, though apparently further emphasis is still desirable, several important points in connection with the clinical interpretation of serologic tests for syphilis, viz

- 1 The clinician desires that the laboratory shall employ a test which is positive in the highest possible percentage of patients infected with syphilis (i e, of maximum sensitivity) but which is uniformly negative in nonsyphilitic individuals (i e, of maximum specificity)

- 2 The several complement fixation (Wassermann) and flocculation tests for syphilis depend on identical physicochemical phenomena and differ from each other only in certain technical details. The flocculation tests, requiring only one ingredient (antigen) in addition to the patient's serum, are simpler to perform than



the complement fixation tests (which require antigen, complement, amboceptor, and sheep or human red cells in addition to patient's serum), but this simplicity of performance is in part counterbalanced by greater difficulty of interpretation, especially in the hands of relatively unskilled technicians

3 No test yet devised is so sensitive as to be uniformly successful in detecting the presence of syphilis or so specific as to avoid an occasional false positive result in a nonsyphilitic person

4 Variations in sensitivity and specificity both may be produced by variations, often minor, in the reagents employed in the test or the physical conditions under which it is performed. In general, however, sensitivity is increased at the expense of specificity, and vice versa. *i e*, it is technically possible to perform a test so sensitive as to be positive on all serums submitted, even those from normal persons, or one so insensitive as to be negative on all serums, even those from patients with secondary syphilis. The best available present-day test should be that which compromises with these technical factors to provide the largest possible number of positive tests in syphilitic patients and the smallest number of positive tests in nonsyphilitic individuals

5 The current custom of reporting the results of serologic tests in terms of plus marks (*i e*, 4+ denoting strongly positive, 3, 2, 1 plus or plus-minus denoting varying degrees of weakly or partially positive, or doubtful, and 0 equaling negative) is inaccurate and misleading. "Four-plus" does not necessarily mean "strongly positive" since all tests in current use are qualitative or only roughly quantitative; that is, they are performed with a fixed amount of whole serum related to the total bulk of the test and ranging from 0.1 to 0.025 cc. Actually, a test may be positive with as little as 0.00005 cc of whole serum. In such a case, if plus marks are to be used in reporting, the result might properly be expressed as "four-thousand-plus" instead of "four-plus." The current terminology of "four-plus" covers a range of positivity extending from 0.1 to 0.00005 cc (or even less). Under these circumstances, it is obvious that plus marks, and the qualifying adjective "strongly," should be eliminated from routine serologic terminology and should be replaced by the single word "positive."

Though "positive" covers an extreme range of variation in terms of the amount of patient's serum employed in the test, the other symbols (+ + +, + +, +,  $\pm$ , *i e*, 3, 2, 1 plus, etc.), commonly used to describe a "partially positive" or "doubtful" result, cover instead an extremely minute range of variation. With the Wassermann test, for example, and with the usual total volume of 1.0 to 1.25 cc, this range is only between the limits of 0.2 and 0.02 cc of whole serum. Within this narrow range, there is no valid excuse for the attempt to report minute variations in the degree of positiveness, and all such results should be expressed by the word "doubtful."

6 Aside from syphilis, the only disease conditions which give positive results with serologic tests for syphilis are yaws, relapsing fever, leprosy (all frequently), and malaria (infrequently). With rare exceptions, positive tests in all other nonsyphilitic individuals are due to technical error (common mistakes which are to be guarded against by repetition and intra- or interlaboratory check) or to biologic phenomena (very rare, and too intricate for discussion here).

7 Doubtful serologic tests may be due to syphilis (*e g*, as a stage in the appearance of reagin—the name given to the substance producing a positive test—early in the disease, or in its disappearance later, either spontaneously or more often under the influence of treatment, at both of which times but a very small

amount of reagin may be present) In nonsyphilitic individuals, doubtful results may be due to technical error, to faulty interpretation, to attempts to increase the sensitivity of a given test beyond its particular limits of safety (all common errors), or to the same biologic phenomena which rarely cause a false positive result

8 In the absence of the disease conditions enumerated in paragraph 6, *a positive serologic result properly controlled for technical and biologic error means that the patient has syphilis*

9 Since no test is as yet so sensitive as to detect all instances of syphilitic infection, *a negative result does not exclude the presence of syphilis*

10 A doubtful result may mean that the patient has syphilis Since this is so, such a result obtained in a nonsyphilitic individual is often as confusing to the clinician as a false positive report

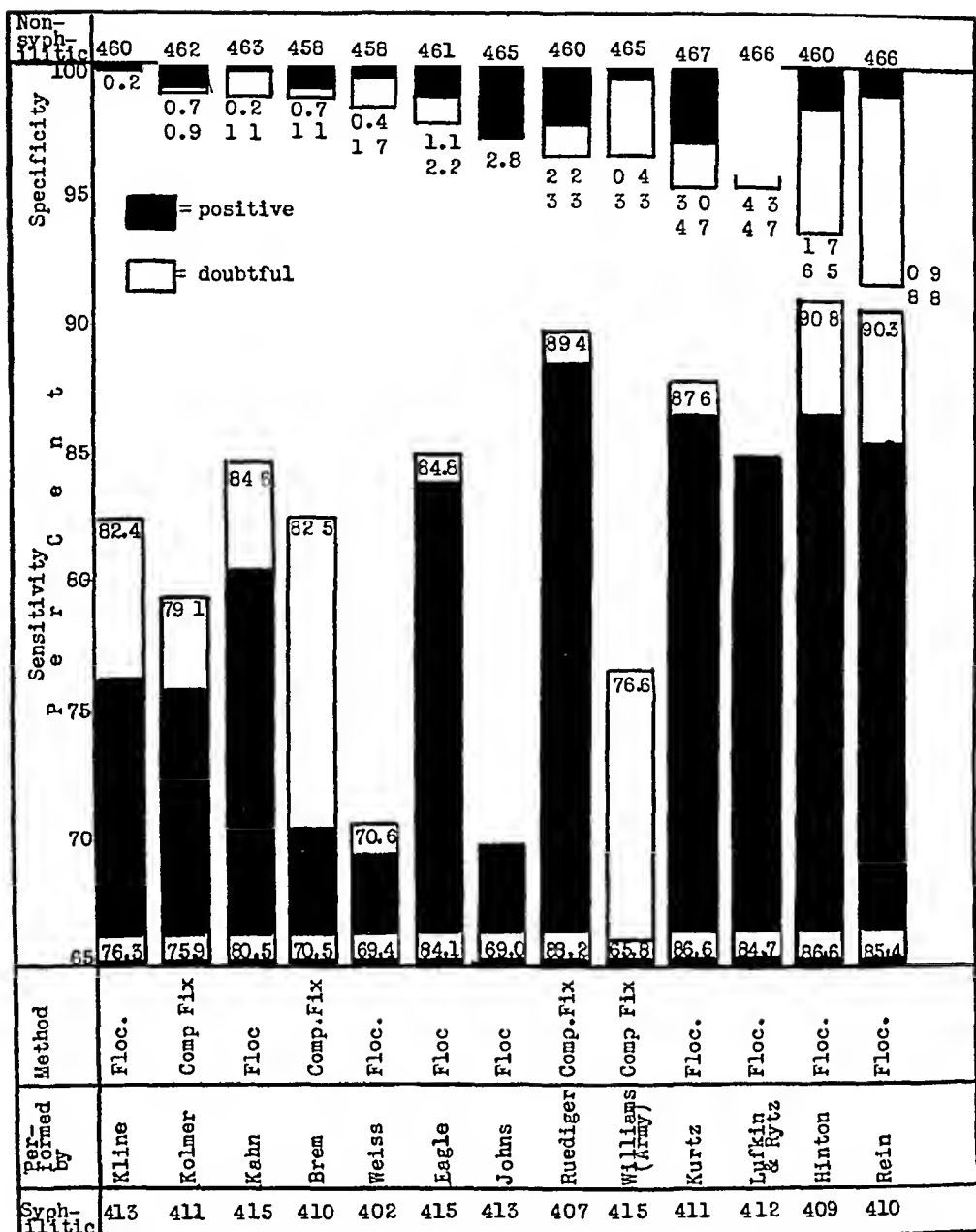
11 The proper person to interpret serologic results is not the serologist, who usually has no contact with the patient, but the clinician, who can fit the laboratory data with history and physical findings Manifestly, the clinician will be better fitted to accomplish this task if he is familiar, not necessarily with the technical details of performing serologic tests, but with the accomplishments and limitations of the test which he is employing

This lengthy introduction is a necessary preliminary to a reconsideration of the results of the American plan for serologic evaluation In this reconsideration and in view of the preceding discussion, the results obtained by the competing serologists have been rearranged to show (1) sensitivity, the percentage of positive *and* doubtful results obtained in the 415 blood specimens from syphilitic patients, and (2) specificity, the percentage of positive *and* doubtful results obtained in the 152 normal nonsyphilitic persons *plus* the 316 presumably nonsyphilitic individuals with other diseases or conditions The increased number of nonsyphilitic serums provides a much more accurate basis of evaluation of specificity

Though it is obvious that a doubtful result in a known syphilitic patient is not as convincing as a positive result, it is nevertheless scorable as a partial success for the competing serologist Conversely, while a false doubtful result in a nonsyphilitic individual is not as disturbing to the clinician as a false positive test, it is nevertheless disturbing enough and as such scorable as a partial failure for the serologic plan in question

To the clinician interested primarily in diagnosis, specificity is a more important factor than sensitivity It is particularly desirable to employ as a routine diagnostic test one which provides the smallest possible number of nonspecific reactions (whether positive or doubtful) in nonsyphilitic persons A diagnosis of syphilis made in an uninfected individual is a disaster of the first magnitude If maximum specificity demands some sacrifice of sensitivity, the clinician is quite willing to accept the sacrifice

Figure 1, therefore, ranks the participating serologists in order of specificity, reading from left to right The sensitivity of each test is also shown in the same figure, in order to permit ready comparisons If one utilizes as a satisfactory standard of specificity that chosen by the serologists (both of the American and the Montevideo Conference), *i e*, less than 1 per cent false positive tests in nonsyphilitic persons, seven tests qualify as satisfactory If, however, false doubtful results are added to the false positives, only four are satisfactory Kline diagnostic, Kolmer complement fixation, Kahn diagnostic, and Brem complement fixation If the second American evaluation study confirms the first, one or more of these four tests should be adopted for routine diagnostic use Of the four, the two most sensitive are the Kahn and Kline flocculation tests



This chart is an adaptation and rearrangement of the chart provided in the final report of the Committee on Evaluation of Serodiagnostic Tests for Syphilis in the United States. The percentage scale has purposely been arranged to run from 65 to 100 per cent, rather than from 0 to 100 per cent, in order to magnify the differences in the results of the competing serologists. The figures below the blocks denoting sensitivity show for each test (the upper number) the incidence of false positive results and (the lower number) the total incidence of false positive plus false doubtful results. The figures within the lower black blocks indicate the percentage of positive results obtained for syphilitic patients, the figures within the lower white blocks show the percentage of positive plus doubtful tests obtained for syphilitic patients. In the lines at the top and bottom of the page labeled nonsyphilitic and syphilitic, the numbers signify the actual number of specimens examined by each serologist. Note that all tests except four were successful in obtaining 80 per cent or more of positive plus doubtful tests in patients with known syphilis and that, in general, there is a tendency for a decrease of specificity corresponding with an increase of sensitivity. For diagnostic purposes the first four tests to the left of the chart are probably preferable, for the increased sensitivity demanded for the special purposes enumerated in the text, the Ruediger complement fixation test and the Hinton and Kline exclusion flocculation tests (Rein) are the methods of choice. (Reproduced from the *American Journal of Syphilis, Gonorrhea and Venereal Diseases* [20 212, 1936] )

Six serologists—Ruediger (complement fixation), and Eagle, Kurtz (Kahn presumptive), Lufkin and Rytz, Hinton, and Rein (Kline exclusion), all of these five latter flocculation tests—have tests of slightly higher sensitivity than the Kline or Kahn diagnostic tests. In each instance, however, this increased sensitivity is achieved at the cost of loss of specificity. Kline and Kahn have recognized this fact in the naming of their more sensitive tests (“presumptive” and “exclusion” tests), but too many clinicians do not realize the inference of these special names. If these results are confirmed by the second American evaluation study, it would be desirable to limit the use of these more sensitive but less specific serologic tests to three sets of circumstances: (1) in the serologic testing of donors for blood transfusion, as an added safeguard for the prevention of transfusion syphilis, (2) as serving special syphilis clinics, where the results are susceptible of expert clinical interpretation, or (3) in following the results of treatment in patients definitely proved to have syphilis. In the absence of such limitations, the clinician served by a laboratory which employs one of them as a routine diagnostic measure must be prepared to accept a risk, ranging from 2 to nearly 9 per cent, of false nonspecific results in nonsyphilitic patients.

Wilson and Levin<sup>17</sup> confirm the fact that malaria may produce false positive results of serologic tests for syphilis. From 1930 to 1934 these authors observed 262 patients with proved malaria, for each of whom were made a Kolmer complement fixation test and either a standard Kahn or a diagnostic Kline flocculation test. On the basis of the history, previous and subsequent serologic tests and physical examination it was decided that 23 of the 70 who manifested positive results certainly, and that an additional 23 probably, had syphilis. For 9 of the remainder the information was inadequate, but 15 (63 per cent of the nonsyphilitic patients) who manifested positive serologic results (there was little agreement between the complement fixation and the flocculation tests, however) were later shown by careful study and follow-up not to have syphilis. In one of these a positive result of a cerebrospinal fluid test was obtained during malaria, the result was later normal. In 7 others of these 15 patients the cerebrospinal fluid was normal.

*The Relationship Between Serologic Tests of the Blood and Those of the Cerebrospinal Fluid*—Unfortunately the Serologic Conference did not specifically consider this point, but in their 307 patients with late syphilis who had had varying amounts of treatment, the highest percentage of positive results of serologic tests was 86.4 (Ruediger, complement fixation), and the tests with higher specificity fell well below this figure. In the light of the incidence of neurosyphilis one does not need the report of Grund,<sup>18</sup> of 5 patients with a negative result of the

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17 Wilson, R. J., and Levin, S. L. Observations on Effect of Malaria on Wassermann Reaction, *Am J M Sc* **191** 696 (May) 1936.

18 Grund, J. L. The Exclusion of Neurosyphilis by Means of the Hinton Reaction of the Blood, *Arch Dermat & Syph* **32** 569 (Oct) 1935.

Hinton type of flocculation test of the blood but a positive result of tests of the cerebrospinal fluid, to conclude that a negative result of a test of the blood serum does not exclude the possibility of involvement of the neuraxis

#### THE SOCIAL AND PUBLIC HEALTH ASPECTS OF SYPHILIS

*Dissemination of Information*—Since the shut-down of the venereal disease control program, which operated effectively both here and abroad during the World War, physicians interested in the control of syphilis have labored against almost insurmountable difficulties. The profession was apathetic, and public ignorance could not be combated because the press forbade the use of the word syphilis or any of its implications.

In the past quintade, however, the profession has been so barraged by the studies of the Cooperative Clinical Group and other contributions derived therefrom or based on similar lines that, in Nelson's<sup>19</sup> opinion

The diagnosis and management of syphilis, and especially of early syphilis, have been written and talked about so much in recent years that there is bound to be trouble ahead for the physician who makes mistakes in diagnosis or who fails to treat the patient properly. Appearance before the Board of Registration in Medicine is the least that can happen. Suits for malpractice will follow as rapidly as the public becomes acquainted with what it has a right to expect from the physician.

Ideally, of course, Nelson is right, practically, he fails to recognize that the apathy of many physicians in regard to syphilis arises from their lack of fundamental training. Clarke and Exner<sup>20</sup> supplement Exner's<sup>21</sup> earlier study on the teaching of syphilology in medical schools by a statistical study of hospital practice in the training of interns. Of 331 hospitals with outpatient departments which responded to inquiry, 243 required service of some or all interns in the clinic for syphilitic patients, in an additional 70 such service was optional, but there were 17 hospitals which did not make the service for syphilitic patients available to their interns! Also, the tour of duty in the hospitals in which this service was required was found to vary widely, with extremes of six and seven hundred and twenty hours of attendance, showing an average of fifty-eight hours distributed over a period of ten weeks. In those hospitals in which service in the clinic for syphilitic patients was

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19 Nelson, N. A. Correspondence Entitled "Trouble Ahead," *New England J. Med.* **213** 941 (Nov. 7) 1935.

20 Clarke, C. W., and Exner, M. J. The Training of Interns in Syphilology, *J. A. M. A.* **106** 767 (March 7) 1936.

21 Exner, M. J. Report on Instruction Regarding Syphilis in American Medical Schools, *Am. J. Syph.* **17** 449 (Oct.) 1933.

optional, the average period of service was somewhat less, and not all hospitals reported that the interns worked under competent supervision

It has long been obvious, however, that granted an adequate level of professional competence, the control of syphilis must necessarily depend largely on dissemination of information to the laity, which has in the past been practically impossible because of the attitude of the press. In the recent past, however, enlightened editors in many of the larger cities have published feature articles and important news items regarding syphilis, and Parran,<sup>22</sup> in a careful summary of the important facts, with a wise avoidance of theatrical effects, reached probably a majority of the reading public.

*Results*—Nelson<sup>23</sup> shows that a determined effort to control syphilis actually accomplishes its aim. Contrasting the situation in Massachusetts for the period 1915 to 1919 with that for 1934, he found a 70 per cent reduction in the number of cases of syphilis among pregnant women, a 30 per cent reduction in the number of patients admitted to clinics for syphilitic treatment and in reports of cases of early syphilis from physicians and hospitals and a 32 per cent reduction in the number of cases of neurosyphilis reported. The incidence of gonorrhea during the same period did not decline.

*The Cost of Syphilis*—Thompson, Brumfield and Caldwell<sup>24</sup> carefully studied conditions in Baltimore and determined that for the year 1933 the direct cost of syphilis to that representative community of 828,000 persons was \$170,000. This does not include any of the indirect costs, which are listed but which could not be determined and were not estimated. Forty-five per cent of this sum was contributed by privately endowed charity. The significant finding was, however, that the bulk of the funds was being expended in the treatment or institutional care of patients with late syphilis, largely with irremediable cardiovascular disease and neurosyphilis, and these authors emphasize that a relatively modest increase in the sums expended for the treatment of early syphilis would soon pay handsome dividends in reducing this load of caring for patients with late syphilis.

*Methods for the Control of Syphilis*—Syphilis has become a rare disease in the Scandinavian countries and is decreasing in extent in Great Britain. In the course of developing adequate facilities for the

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22 Parran, T, Jr. The Next Great Plague to Go, *Survey Graphic* **25** 405 (July) 1936. Why Don't We Stamp Out Syphilis? *Reader's Digest* **29** 65 (July) 1936.

23 Nelson, N. A. The Decreasing Prevalence of Syphilis in Massachusetts, *J. A. M. A.* **106** 105 (Jan 11) 1936.

24 Thompson, W. C., Brumfield, W. A., and Caldwell, L. The Direct Cost of Syphilis in a Representative American City, *Am. J. Syph., Gonorr. & Ven. Dis.* **20**:243 (May) 1936.

control of syphilis in the city of New York, a committee, headed by Dr John L. Rice, the Commissioner of Health, during the summer of 1935 visited Scandinavia and Great Britain to investigate the methods used there. The general conclusions stated in the detailed report<sup>25</sup> were as follows:

In each of the countries studied by the Commission, there appears to have been a downward trend in the prevalence of syphilis since the peak in 1919 or 1920. The prevalence of gonorrhea has shown less change and may be said to have remained comparatively unaffected by the measures which have been taken in the several countries.

Several causes are believed to have played an important part in the decrease of syphilis. First and most important are believed to be the basic scientific fact that treatment renders syphilis noninfectious and the fact that in all of these countries diagnosis and treatments are free, accessible, and generally good. At the beginning of the downward trend, when the descent was sharpest, natural causes played an important part. The epidemic had spent its force. Vigorous health propaganda also led infected persons to seek treatment and so to become noninfectious, and warned uninfected people to avoid infection. It is impossible to allocate to these various factors their appropriate ratio of credit for the reduction of syphilis, but it is generally believed in Great Britain and the Scandinavian countries that prompt and adequate treatment of infectious cases was most important.

In Sweden and Denmark diagnosis and treatment are provided at the expense of the state. In Great Britain they are at the expense of the state and the local governmental units. In Norway, for the most part, they are provided as a feature of the health insurance scheme. In all countries diagnosis and treatment are free to all without economic distinction.

In Sweden, Norway, and Denmark an important feature for the plan of combating syphilis and gonorrhea is ample facilities for hospitalization. A large proportion of infectious cases in these countries is hospitalized. In Great Britain proportionately fewer cases are given hospital care.

Public health measures for the control of syphilis and gonorrhea in all the Scandinavian countries are based on the principle that these diseases are communicable and should be dealt with as such. The law requires the reporting of cases, obligates patients to receive treatment, gives health authorities the power to enforce medical care including hospitalization if necessary, penalizes the knowing transmission of infection, and authorizes the finding and the bringing under control of all sources of infection and of all delinquent patients. While persuasion is usually successful, coercive measures are provided for that very small proportion of patients who are uncooperative. In Great Britain, on the other hand, syphilis and gonorrhea are not reportable and not quarantinable, treatment is entirely voluntary, and the health authorities have no power to intervene for the protection of the public health even with the most infectious and uncooperative cases.

If a comparison is made briefly between the Scandinavian countries and Great Britain on the one hand, and the United States on the other, it is seen that our

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25 Clarke, C. W. Control of Syphilis and Gonorrhea in the Scandinavian Countries and Great Britain. A Report of the New York City Commission to Investigate the Prevention and Control of Syphilis and Gonorrhea in Scandinavian Countries and in Great Britain, *Am J Syph, Gonorr & Ven Dis* 20:1 (July, pt 2) 1936.

policy and practices more nearly resemble those of the Scandinavian countries, for we have all the legal powers of those countries to deal with syphilis and gonorrhea as communicable diseases. Unlike the Scandinavian countries and Great Britain, there are not in the United States free and accessible facilities for the diagnosis and treatment of syphilis and gonorrhea regardless of economic status. The critical problem in America may be said to be that of overcoming these obstacles and bringing all infectious cases of syphilis and gonorrhea, regardless of economic status, under medical care.

Rietz,<sup>26</sup> who is Commissioner of Health in Stockholm, reports in detail the mechanism of the control of venereal disease in Sweden. The backbone of the program is a law, passed in 1918, which contains the following specific points:

- 1 Every person suffering from venereal disease must submit to treatment by a physician and must follow his directions.

- 2 Every such person has the right, irrespective of the size of his income, to obtain free medical treatment and medicine, in case he is not being treated by a private physician. This includes free injections, free serologic examinations, as well as free certificates required by the public health authorities as to complete recovery or continued treatment. Hospitalization in a special general ward is also furnished free of charge.

- 3 Every physician treating a new case of venereal disease must try to obtain information about the source of infection.

- 4 Against patients who do not properly follow up their treatment and against individuals identified as the source of infection but unwilling to come to treatment certain compulsory measures may be taken.

- 5 A person who knows that he or she suffers from venereal disease and who by carelessness causes its transmission is subject to punishment of a severity up to forced labor.

- 6 Every marriage partner prior to obtaining a marriage license has to sign a statement certifying his or her freedom from venereal disease in a contagious stage.

- 7 The local public health authorities must publish information about the existence of the clinics for the treatment of venereal diseases.

Added to this has been the most determined search for every source of infection until now, from a peak of 44 new cases of syphilis per year per ten thousand population, the rate has dropped to less than 2 per ten thousand in Stockholm. The disease has virtually disappeared in the rural districts.

A committee of experts, cooperating with the United States Public Health Service, has recently drawn up a series of recommendations for a program for the control of venereal disease.<sup>27</sup> They recommend that

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<sup>26</sup> Rietz, E. The Prevention of Venereal Disease in Sweden, *Am J Pub Health* **26** 357 (April) 1936.

<sup>27</sup> Vonderlehr, R. A., and others. Recommendations for a Venereal Disease Control Program in State and Local Health Departments, *Ven Dis Inform* **17** 1 (Jan) 1936, *J A M A* **106** 115 (Jan 11) 1936.



from the administrative side such a program should be under the full time direction of an officer for the control of venereal disease but should be closely coordinated with the division for communicable diseases, of the health department and with members of the medical profession and social service agencies and that the allocation of funds for the control of venereal disease be in proportion to the magnitude of the problem in the given locality. Facilities for treatment must be provided which are adequate to provide diagnosis and emergency treatment of any patient who applies, to care for any patient referred by a physician either for treatment or for consultative advice and to provide treatment for all who cannot afford to pay. In large centers the subsidy of existing large clinics rather than the establishment of new isolated units is advised, and the details of how best to accomplish these desiderata in rural communities are given.

The committee emphasizes the necessity of a routine serologic test for syphilis in pregnancy, preferably more than once, points out the desirability of epidemiological work both in the finding of contacts and in the tracing of patients who have lapsed and stresses the necessity for adequate laboratory facilities for diagnosis and treatment. An informative educational program, both for the laity and for the profession, is advised, and finally the results of such a program should be checked, both by accurate mortality and morbidity data and by more elaborate statistical surveys.

Parran<sup>28</sup> indicates that such a program has largely been placed in effect in the state of New York, and Massey<sup>29</sup> indicates that portions of such a program are applicable to a rural county of Maryland in which syphilis is prevalent. Reinhard and Fales<sup>30</sup> describe the technique of follow-up used by the health department in Baltimore and show that efforts to follow the delinquent and persuade (or occasionally force) the recalcitrant patients are far from fruitless.

As a rule, the American authorities favor avoidance of compulsion, such as the Ontario regulations<sup>31</sup> include, preferring education and persuasion as probably slower but more certain methods of accomplishing the eventual eradication of syphilis. There are many who have had a large experience with persons in the lower strata of society, however,

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28 Parran, T, Jr. Syphilis Control in New York State, *Ven Dis Inform* **16** 303 (Sept) 1935

29 Massey, B. Twelve Months' Syphilis Control Effect in a Rural County, *Ven Dis Inform* **17** 151 (June) 1936

30 Reinhard, F O, and Fales, W T. Delinquent Patients in Venereal Disease Clinics, *J A M A* **106** 1377 (April 18) 1936

31 Pequegnat, L A. The Applied Aspects of the Venereal Disease Legislation of Ontario, *Canad Pub Health J* **27** 228 (May) 1936

who, viewing Sweden's record in the control of syphilis with envy, listen sympathetically to Rietz <sup>26</sup> when he says

Though personal liberty is safeguarded in Sweden at least as carefully as in America, the law imposes a very definite restriction of freedom upon persons afflicted with venereal disease, compelling them to accept an amount of medical treatment, not according to their own choice, but according to the decision of responsible physicians. Upon individuals, under such control and to whom complete medical facilities for treatment are available at no cost, the nation further imposes the responsibility not to propagate the disease. For willful neglect of this responsibility, punishment up to the severity of forced labor can be imposed.

Finally, Vonderlehr <sup>32</sup> reemphasizes that the crux of the control of syphilis is the adequate treatment of early syphilis, by no other known means may the incidence of syphilis be materially reduced. With the adequate treatment (which necessitates early diagnosis) of early syphilis, it would be possible in a short generation to duplicate the Scandinavian record.

#### DRUGS

*The Investigation of New Drugs Designed for the Treatment of Syphilis*—Snodgrass <sup>33</sup> clearly restates the conditions which must be fulfilled before any judgment may be rendered as to the applicability of a new drug to the treatment of syphilis in human beings

- 1 An ample supply of the drug must be furnished the investigator, and unlimited time must be allowed for the investigation.
- 2 All details of chemical composition and chemical stability must be known.
- 3 The technic of administration, i. e., the route, special solvents required and unusual methods to be employed, should have been worked out by the manufacturer.
- 4 Then, by means of animal experimentation
  - (a) The lethal dose unit of drug per animal weight and mode of death must be determined.
  - (b) The toxic manifestations, early and late, of a sublethal dose should be determined.
  - (c) Histopathologic studies of the organs of animals killed by the drug and of animals given sublethal doses should be made to determine masked effects on important organs.

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32 Vonderlehr, R. A. The Control of Syphilis with Special Emphasis on Adequate Treatment as a Control Measure, *Ven Dis Inform* **16** 413 (Dec) 1935.

33 Snodgrass, W. R. Methods to Be Employed in the Investigation of New Substances Designed for the Treatment of Syphilis, *Brit J Dermat* **48** 11 (Jan) 1936.

- (d) Efforts should be made to determine the cause of reactions, and means should be sought to prevent or to treat them
  - (e) The therapeutic index, i e., the minimum lethal dose/ the minimum curative dose, should be determined for rabbits with syphilis
  - (f) The incidence of relapse in rabbits with syphilis after treatment should be noted
- 5 If the results of animal experiments are favorable, clinical trial on human beings with syphilis is justified if appropriate safeguards to the patient and proper control of the observations are provided
- (a) Patients with early syphilis should not be subjected to an untried method of treatment
  - (b) The toxicity of the drug for man should be determined by giving, at the outset, one twentieth of the theoretical dose determined by animal experiment to patients with late syphilis, preferably those who have had previous treatment, and only when the patient consents to the trial of a new drug. If no reactions occur, the dose may be increased
  - (c) The effect on the serologic titer and on mensurable lesions of late syphilis should be observed. If these are favorable, trial on patients with early syphilis is justified
- 6 In treating patients with early syphilis with a drug under trial
- (a) The rapidity of disappearance of *S. pallida* from lesions should be observed
  - (b) The rapidity of healing should be noted and compared with that in patients under established systems of treatment
  - (c) The serologic titer should be followed and similarly compared
  - (d) Patients treated with a new drug should have a particularly careful, long follow-up with regard to clinical or serologic relapse

*Mercury*—Dissatisfied with the evidence on which bismuth has been adjudged more potent than mercury in the treatment of syphilis, Cannon and Robertson<sup>34</sup> sought to reexamine the subject. Unfortunately, their series was small, their controls were inadequate and they chose for comparison preparations of heavy metals which are not generally conceded

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34 Cannon, A. B., and Robertson, J. The Choice of Bismuth or Mercury with Arsphenamine in the Treatment of Early Syphilis, *J. A. M. A.* **106** 2133 (June 20) 1936

to be the most effective (an oil suspension of sodium potassium bismuth tartrate and an oil suspension of mercuric salicylate) They state their conclusions as follows

1 The salts of both metals have an important place in the antisyphilitic armamentarium The various preparations selected—both of bismuth and of mercury—appear to have justified themselves in all cases examined in which the treatment was regular and the dosage adequate, but neither metal can compensate for the disadvantage of using an inferior arsphenamine preparation

2 Mercury gives more brilliant but less uniform results than bismuth, so that in robust patients with a healthy excretory mechanism the body's natural defenses are perhaps more effectively stimulated by the mercurials For patients less vigorous and for those who do not respond well to mercury preparations, bismuth offers a valuable substitute

3 Arsphenamine can be counted on to deliver the strongest initial attack against *Spirochaeta pallida* and acts to best advantage when reinforced by one of the heavy metals, but if for any reason an arsphenamine is contraindicated, bismuth will probably give the better performance alone

4 For those who would minimize the chances of ill effects and for those who hold that the parasite may become drug fast, alternating the two metals offers an obvious advantage

*Bismuth*—As was forecast,<sup>1</sup> a bismuth preparation intended for oral administration has been introduced under the name bismutrat and unfortunately has been exploited in a way which leaves much to be desired Careful studies of its applicability in rabbit syphilis have been made, however, by Rein and Sulzberger<sup>35</sup> and by Kemp and Rosahn<sup>36</sup> Rein and Sulzberger observed only a small group of animals and themselves recognize that their conclusions are therefore subject to some question, but they were sufficiently impressed with the action of bismutrat in rabbit syphilis to consider further experimental work advisable Kemp and Rosahn, however, found that twenty-four daily doses each of bismutrat containing 20 mg per kilogram of metallic bismuth failed to alter materially the course of early syphilis in 5 of 6 animals treated, and similar administration of doses of 50 mg per kilogram apparently suppressed the infection in 2 of 4 animals but cured none Similar experiences were noted with the oral administration of bismuth sodium mon citrate and bismuth and potassium tartrate Important as are these observations, the greatest contribution made by these authors was their

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35 Rein, C R, and Sulzberger, M B Bismuth by Mouth in the Treatment of Syphilis A Preliminary Experimental Study with Bismuth Chloride (Bismutrate) in Rabbit Syphilis, Am J Syph, Gonorr & Ven Dis 20 125 (March) 1936

36 Kemp, J E, and Rosahn, P D The Oral Administration of Bismuth in the Treatment of Experimental Rabbit Syphilis, Am J Syph, Gonorr & Ven Dis 20 131 (March) 1936

emphatic restatement of the fact that by virtue of the entirely different chemical conditions existing in the gastro-intestinal tracts of the rabbit and man, the rabbit is entirely unsuited for the evaluation of preparations intended for oral administration in the treatment of syphilis in man. Finally, they conclude "Until there is available a more adequate method of determining the value of this form of treatment, it is unwise to suggest the oral use of bismuth salts in the treatment of late syphilis, and reprehensible to suggest their use in the treatment of early syphilis."

Kolmer<sup>37</sup> investigated the possibility of administering bismuth by inunction by rubbing daily 50 mg per kilogram of bismuth and potassium tartrate into the backs of normal and syphilitic rabbits. No toxic symptoms developed after six weeks of this treatment in the former group, and no influence on the course of events was noted after four weeks of treatment in the rabbits with syphilis.

*Thio-Arsene*—Utilizing the patented method of Kharasch for the production of thioarsenites from the combination of an arsenoxide with a thio acid, Eckler and Shonle,<sup>38</sup> in an investigation of twenty compounds, found one, disodium bis (parasulfophenyl) (acetamidophenyl)-dithio-arsenite, which for the sake of brevity they called thio-arsene, which from preliminary study seemed worth investigating further. The present paper details and satisfactorily reports the chemical and basic pharmacologic investigations necessary before considering a new arsenical in the treatment of syphilis in man. Clinical investigation of the drug was undertaken by three groups. Becker and Obermayer<sup>39</sup> substituted thio-arsene for arsphenamine in a conventional arsphenamine-bismuth system of treatment, and on the basis of 4,000 injections given to 291 patients with various forms of syphilis they conclude "The advantage of low arsenical content, along with good trypanocidal efficiency and low toxicity, coupled with the fact that the drug is available in solution in ampules, entitles thio-arsene to serious consideration in syphilotherapy in combination with bismuth." They observed gastrointestinal reactions in from 20 to 30 per cent of their patients but state that the incidence of such reactions was reduced more than 50 per cent by slowing the rate of injection. Jaundice was observed in 8 patients, no other reactions occurred.

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37 Kolmer, J. A. Inunctions of Bismuth in the Treatment of Experimental Syphilis of Rabbits, *J. Chemotherapy* **12** 278 (Oct.) 1935.

38 Eckler, C. R., and Shonle, H. A. A Preliminary Study of Thio-Arsene, Disodium Bis (P-Sulfophenyl) (Acetamidophenyl)-Dithio-Arsenite, *Am. J. Syph. & Neurol.* **19** 495 (Oct.) 1935.

39 Becker, S. W., and Obermayer, M. E. Clinical Observations on the Treatment of Syphilis by a Combination of Bismuth Salicylate and a New Arsenical Synthetic. A Preliminary Report, *Am. J. Syph. & Neurol.* **19** 505 (Oct.) 1935.

Connor and his co-workers<sup>40</sup> employed the drug alone for the treatment of patients with various stages of syphilis and discovered that it was not well tolerated, less than half of 206 patients studied for tolerance were able to stand doses of 5 cc or more. No serious reactions, however, were encountered. The clinical results were unsatisfactory in 12 (24 per cent) of 49 patients with early syphilis, and in 10 of 27 patients *S pallida* was found in the lesions by dark field examination on the third day after treatment was begun. They conclude

Thio-arsene does not possess a high degree of therapeutic efficiency even when administered biweekly in the highest tolerated doses

It is probably not a suitable drug for the treatment of syphilis, especially since more efficient and better tolerated drugs are at hand

In drawing the above conclusions as regards the therapeutic efficiency of thio-arsene, it is to be emphasized that they are data based on the use of thio-arsene alone and not on data of thio-arsene combined with other forms of therapy

Robinson and Moore<sup>41</sup> report an even less happy experience, which is summarized as follows

In the form in which thio-arsene was supplied to us, its use was followed by such a high incidence of severe gastro-intestinal reactions as to necessitate marked reduction of the advised dose, and even with this reduction in dosage, severe though not serious gastro-intestinal reactions occurred in such a large proportion of cases as to render patients unwilling to continue treatment with the drug. Thio-arsene is not utilizable in patients who have previously been sensitized to the arsphenamines. In our hands a fresh dermatitis was provoked by thio-arsene in seven of eleven such patients. As to therapeutic efficacy, thio-arsene compares unfavorably with any of the arsphenamines or with bismuth as to its effect on the disappearance of surface organisms, on the healing of lesions, and on the blood Wassermann reaction

It is, we believe, unwise to draw conclusions as to the efficacy of any anti-syphilitic drug when used in combination with any other. In order to prove the efficacy of thio-arsene used in combination with bismuth, the procedure followed by Becker and Obermayer, it would be necessary to study the results of treatment in a similar and parallel series of patients treated with bismuth alone. This has not been done. In our opinion, the favorable results secured with the thio-arsene-bismuth combination employed by Becker and Obermayer are probably largely attributable to bismuth rather than to thio-arsene. Thio-arsene, in its present form, is not entitled to serious consideration in syphilotherapy

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40 Connor, W. H., Shaw, H. C., Levin, E. A., and Palmer, R. B. The Therapeutic Value of Thio-Arsene. A Clinical Study of the Therapeutic Efficiency and Toxicity of Disodium Bis (P-Sulphophenyl) (Acetamidophenyl)-Dithio-Arsenite, Based on 2,282 Injections Administered to 251 Patients with Syphilis, *Am J Syph & Neurol* **19** 514 (Oct) 1935

41 Robinson, H. M., and Moore, J. E. The Treatment of Syphilis with a New Arsenical Drug (Thio-Arsene), *Am J Syph & Neurol* **19** 525 (Oct) 1935

*Mapharsen*—The basic work of Tatum and Cooper <sup>42</sup> referred to in the previous review <sup>1</sup> has been followed by detailed pharmacologic study by two groups, Raiziss and Severac <sup>43</sup> and Gruhzit <sup>44</sup>. These investigators, working independently, arrived at essentially similar figures for the curative index of mapharsen in trypanosomiasis in rats (7.2 and 9, respectively), but whereas Gruhzit found a therapeutic index of 7 for mapharsen in rabbits with syphilis, Raiziss and Severac obtained the low figure of 0.92. The latter, therefore, concludes "the clinical use of this drug in adequate curative doses might be fraught with considerable danger."

Since Gruhzit's results indicated a superiority over the brand of neoarsphenamine with which it was contrasted (a curative index for syphilis in rabbits of 4 for mapharsen and 3.75 for neoarsphenamine in single dose, but 4.6 and 1.67 for the two drugs, respectively, in multiple doses) several groups of clinicians deemed it worthy of clinical trial, one report of these trials has appeared. Foerster and his associates <sup>45</sup> report eighteen months' experience with mapharsen, during which 4,666 intravenous injections of the drug were given to 233 persons with syphilis and 133 injections were given to 41 normal subjects or sufferers from other diseases. Studies on the excretion of arsenic revealed no undue retention, and dark field follow-up study of lesions in which *S. pallida* had been demonstrated revealed a disappearance of surface organisms usually in twenty-four hours. Healing of visible lesions was prompt, and the serologic response of patients with early syphilis was good. Clinical and serologic relapse were observed in general only after irregular or obviously inadequate therapy or in cases of involvement of the neuraxis. The drug was well tolerated, no nitritoid reactions were observed, and the only immediate reactions were mild gastrointestinal disturbances. Jaundice developed in 4 patients. These authors conclude, therefore, that mapharsen is a potent antisyphilitic agent and should be given an extensive, long time study.

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42 Tatum, A. L., and Cooper, G. A. An Experimental Study of Mapharsen (Meta-Amino-Para-Hydroxy Phenyl Arsenic Oxide) as an Antisyphilitic Agent, *J. Pharmacol. & Exper. Therap.* **50** 198, 1934.

43 Raiziss, G. W., and Severac, M. Comparative Chemotherapeutic Studies of "Arsenoxide" (3-Amino-4-Hydroxy-Phenyl-Arsenoxide) and Neoarsphenamine, *Am. J. Syph. & Neurol.* **19** 473 (Oct.) 1935.

44 Gruhzit, O. M. Mapharsen ("Arsenoxide") in the Therapy of Experimental Syphilis and Trypanosomiasis, *Arch. Dermat. & Syph.* **32** 848 (Dec.) 1935.

45 Foerster, O. H., McIntosh, R. L., Wieder, L. M., Foerster, H. R., and Cooper, G. A. Mapharsen in the Treatment of Syphilis, *Arch. Dermat. & Syph.* **32** 868 (Dec.) 1935.

UNTOWARD EFFECTS OF TREATMENT <sup>46</sup>

In a general article Rajam <sup>47</sup> reports his experience with reactions and complications in the course of the administration of 24,550 doses of neoarsphenamine to 7,160 East Indians with syphilis. His statement that this race does not tolerate neoarsphenamine well is borne out by his figures. Dermatitis was produced in 1 of each 126 patients treated, and the ratio of incidence was 1 to 147 for men and 1 to 83 for women. The individual dose of neoarsphenamine never exceeded 0.3 Gm., yet there was 1 case of dermatitis for each 431 injections. 1 to 514 for the men and 1 to 264 for the women. There were 3 deaths. Jaundice, however, was less than half as common, but in this series hemorrhagic encephalitis developed in 6 cases.

After a somewhat similar study van Putte <sup>48</sup> reports that 10 per cent of his patients at the Batavia Hospital showed cutaneous reactions or allergic phenomena, usually after the third injection of neoarsphenamine.

*Bismutha*—Lueth and his co-workers <sup>49</sup> report a dramatic case of extensive pigmentation of the skin resembling argyria. The patient had for many years taken large quantities of bismuth salts by mouth for the treatment of gastro-intestinal disease. Bismuth was demonstrated by biopsy of the skin. Gougerot and Blum <sup>50</sup> report a similar case in a patient who had been receiving a bismuth compound intramuscularly for the treatment of syphilis over a period of five years.

*Bismuth Erythroderma*—Nicolas, Rousset and Colas <sup>51</sup> review the meager literature on dermatitis following the intramuscular administration of a bismuth compound and add a report of a man of 39 who had severe erythroderma after the eighth dose of bismuth.

*Bismuth Arthralgia*—Genner <sup>52</sup> noted the frequency of complaints of pains in the joints, usually multiple, in patients under antisyphilitic

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46 A large number of individual cases of well recognized complications of treatment have been reported which are not included here.

47 Rajam, R. V. Some of the Major Complications in Treatment of Syphilis, Indian M. Gaz. **70** 661 (Dec.) 1935.

48 van Putte, P. J. Sensibilisatiestoornissen door neosalvarsaan tijdens de antisyphilitische Kuur, Nederl. tijdschr. v. geneesk. **80** 2133 (May 16) 1936.

49 Lueth, H. C., Sutton, D. C., McMullen, C. J., and Muehlberger, C. W. Generalized Discoloration of Skin Resembling Argyria Following Prolonged Oral Use of Bismuth, Arch. Int. Med. **57** 1115 (June) 1936.

50 Gougerot, H., and Blum, P. Imprégnation bismuthique cutanée générale. Pseudoargyrie cutanée provoquée par le bismuth, Bull. Soc. franç. de dermat. et syph. **42** 276 (Feb.) 1935.

51 Nicolas, J., Rousset, J., and Colas, J. Bismuth erythrodermia, Bull. Soc. franç. de dermat. et syph. **43** 9 (Jan.) 1936.

52 Genner, V. Arthralgic Symptoms in the Course of Therapy of Syphilis with Arsphenamine and Bismuth, Nord. med. tidskr. **10** 1753 (Nov. 2) 1935.



treatment, and by a combination of clinical observation and statistical research he concludes that this must be regarded as a complication of bismuth therapy

*Arsphenamine Jaundice*—Sager<sup>53</sup> reports 99 cases of postarsphenamine jaundice, and in a long discussion of the various hypotheses as to etiology which have been advanced, he concludes that the jaundice is related to arsphenamine therapy. If syphilis plays any rôle, it must do so rarely, in his opinion, and while he believes that catarrhal jaundice and postarsphenamine jaundice are not etiologically related, he is willing to concede that there may be summation of the two conditions

*Hepatic Complications*—Using the rose bengal method, Kellogg, Epstein and Kerr<sup>54</sup> studied the hepatic function of 90 patients with syphilis before and during antisyphilitic therapy. Thirty-eight patients had early syphilis, 35 had latent syphilis and 17 suffered from various forms of late syphilis. In 20 of the 90 the result of the rose bengal test was abnormal before treatment was begun, but there was no correlation between this finding and the type of syphilis involved. In 17 of the 20 there were no other signs of hepatic dysfunction, and the results of the rose bengal test were more nearly normal after antisyphilitic therapy in 10 but remained abnormal in 7. The one patient with clinically recognizable cirrhosis of the liver who received arsenical therapy tolerated it poorly. Routine antisyphilitic therapy occasioned a decrease in the excretion of rose bengal in 5 of 29 normal patients who were followed through treatment and accentuated a preexisting hepatic dysfunction in 4 of 18 patients.

*Fat Embolism Following Treatment with Bismarsen*—Swartz, Tolman and Levine<sup>55</sup> report the instance of a patient who, immediately after the third dose of bismarsen became weak, pale and nauseated and a few minutes later had a chill, complained of backache and went into shock. Deep jaundice developed in a few hours, and there were purpuric manifestations and a high grade of nitrogen retention. The patient died twenty hours after the injection. At autopsy little was to be seen grossly, but microscopic study revealed the typical picture of fat embolism.

*Intravenous Testing for Arsphenamine Sensitivity*—Dissatisfied with the unreliability of the patch test (especially when negative results

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53 Sager, R. V. Factors Responsible for Jaundice in Syphilis, with Special Reference to the Rôle of the Arsphenamines, *Arch Int Med* **57** 666 (April) 1936

54 Kellogg, F., Epstein, N. N., and Kerr, W. J. Hepatic Complications in the Treatment of Syphilis. II. Incidence of Hepatic Disease in Patients with Untreated Syphilis and During Their Subsequent Treatment, *Ann Int Med* **9** 1561 (May) 1936

55 Swartz, J. H., Tolman, M. M., and Levine, H. Fatality Following Bismarsen Therapy, *Arch Dermat & Syph* **33** 874 (May) 1936

are obtained) in determining the question of the advisability of further arsenical therapy for patients with a history of postarsphenamine dermatitis, Robinson<sup>56</sup> examined the feasibility of intravenous testing on 110 such patients. At least three months after the dermatitis had subsided each patient was given intravenously 0.025 Gm or less of a different member of the arsphenamine group than the one which was given preceding the reaction and was carefully observed. If the drug was well tolerated, a week later the dose was doubled, and so on until a therapeutic dose was reached. At any stage subjective or objective cutaneous reactions constitute a positive reaction and preclude proceeding further. The most strongly positive reactions were sufficiently mild to occasion the patient no harm and little discomfort.

Forty-four of the patients tested had also had patch tests made, the comparative results are presented for 41. Seven of the 8 who showed a positive result of the patch test and also 21 of the 33 who showed a negative result of the patch test gave a positive reaction to intravenous testing. There were 66 patients tested intravenously who had not had patch tests. Of these, 34 gave negative reactions, and arsphenamine therapy was resumed without event, 21 gave strongly positive reactions, and a group of 11 patients, who at first gave mildly positive reactions, on repetition of the test failed to react.

From this experience the author concludes that a strongly positive reaction to a patch test precludes the further administration of any of the arsphenamines, but that a weakly positive or negative result of a patch test demands that intravenous testing be carried out before a final decision is made regarding the advisability of further arsphenamine therapy.

*Intracranial Hemorrhage After Cisternal Puncture*—Weissenbach and his collaborators<sup>57</sup> report the instance of a patient on whom, a first attempt at cisternal puncture having been unsuccessful, a successful puncture a few minutes later revealed bloody fluid. A severe meningeal reaction developed, but recovery ensued. This occasioned a review of the literature, from which the investigators concluded that there are about 2 serious or fatal complications for every 1,000 cisternal punctures performed, an incidence too high to justify utilization of the method as a routine procedure.

Dandy<sup>58</sup> reports the operative treatment in a similar situation. Technically perfect cisternal puncture revealed a freshly bloody fluid,

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<sup>56</sup> Robinson, H. M. Intravenous Testing in Postarsphenamine Dermatitis, *South M J* **29** 411 (April) 1936.

<sup>57</sup> Weissenbach, R. J., Bocage, A., and Block-Michel, H. Hemorragie meningée au cours d'une ponction sous-occipitale, *Bull Soc franç de dermat et syph* **42** 785 (May) 1935.

<sup>58</sup> Dandy, W. E. The Treatment of Intracranial Hemorrhage Resulting from Cisternal Puncture, *Bull Johns Hopkins Hosp* **56** 294 (May) 1935.

within half an hour the patient complained of headache and drowsiness and shortly thereafter lapsed into coma. Two and a half hours after the puncture he was desperately ill, four hours later craniotomy was performed, and the bleeding point was cauterized, with eventual recovery. At operation it was discovered that the cerebellar tonsils lay much farther down than usual and so had practically obliterated the cisterna. This resulted in placing a posterior inferior cerebellar artery directly in the normal course of the needle. Anatomic study revealed that this is not an unusual anomaly, so Dandy concludes that cisternal puncture carries with it an unavoidable risk.

#### THE PROPHYLAXIS OF SYPHILIS

*Bismuth Prophylaxis*—Inspired by empirical reasoning and encouraged by the experimental work of Levaditi and his collaborators, previously mentioned,<sup>1</sup> Sonnenberg<sup>59</sup> has for nine years been practicing the bismuth prophylaxis of syphilis among prostitutes. His method comprises the weekly injection of 1 cc or more usually, the biweekly injection of 2.5 cc of a 10 per cent suspension of bismuth subnitrate in oil. Twenty-seven of the 327 prostitutes so treated and observed for more than five years have acquired syphilis, in every instance before the fourteenth week of biweekly treatment. Since syphilis is practically universal among the prostitutes of his district, Sonnenberg feels that his experience is absolutely proof of the efficacy of bismuth prophylaxis, and since all the cases of infection occurred before the fourteenth week (the seventh treatment) he concludes that approximately 7 injections of the magnitude he employed are necessary to insure that the tissue bismuth is at a prophylactic level.

Lépinay<sup>60</sup> reports a similar experience on a smaller scale, 38 of 40 persons were protected for periods up to twenty-seven months of regular treatment. He shows, however, that, irrespective of the amount of previous treatment, prophylactic efficiency lasts for only about twenty days after the last injection. Levaditi and his group of workers<sup>61</sup> have continued the experimental work previously commented on<sup>1</sup> but have added nothing new. Levaditi<sup>62</sup> has been urging further clinical trial of the method.

59 Sonnenberg, E. Neuf ans de traitement preventif bismuthique de la syphilis, *Bull Acad de med, Paris* **114** 374, 1935.

60 Lépinay. Essais de preservation de la syphilis par bismutho-prevention chez les prostituees d'un "quartier reserve," *Prophylax antiven* **8** 230 (April) 1936.

61 Levaditi, C., Manin, Y., Seveaux, A., and Vaisman, A. Recherches sur la metalloprevention de la syphilis l'arsenic, *Bull Soc franç de dermat et syph* **42** 1624 (Nov) 1935.

62 Levaditi, C. La metalloprevention de la syphilis, *Prophylax antiven* **8** 195 and 235 (April) 1936.

*Mercury Prophylaxis*—Schereschewsky<sup>63</sup> advances the opinion that mercury is valueless for the prophylaxis of syphilis but states that he has found a 40 per cent ointment of quinine hydrochloride to be unfailing. Millspaugh,<sup>64</sup> however, in a better documented communication reemphasizes the time factor in the prophylaxis of syphilis and corroborates the experiences during the World War that apparent failures of prophylaxis with mercury are traceable to too long an interval between the first exposure and the prophylaxis. Mahoney,<sup>65</sup> in an important paper which is too long to review here in detail, subjected the matter of prophylaxis to experimental resurvey. By three methods of investigation he demonstrated that actual invasion of the mucosa of the penis of the rabbit by the organism after exposure to the virulent emulsion of *S. pallida* took place between the second and the third hour after exposure began, prior to that the organism lay on the surface and could easily be destroyed by antiseptics, and almost as readily by soap and water. Ointment of mild mercurous chloride (in large amounts) served to protect animals from infection if applied before or immediately after exposure and was almost as effective when rubbed into the back as when applied to the area which had been exposed to infection.

#### THE TREATMENT OF EARLY SYPHILIS

In 1928 the Health Organization of the League of Nations sponsored a statistical investigation of the results of the treatment of syphilis in clinics of five countries—France, Germany, Denmark, Great Britain and the United States. The method of gathering material and the plan of study were identical with those of the Cooperative Clinical Group.<sup>1</sup> Ninety-four clinics in these five countries contributed 25,623 case records for analysis. This material was reviewed under Martenstein's<sup>66</sup> able direction, and a report is submitted, based primarily on the results of treatment of 13,198 patients with early syphilis for whom complete information was furnished. In summarizing the experience Martenstein says:

I would therefore repeat once more the unexpectedly clear result that has emerged from this statistical compilation:

The methods of treating primary, and early and late secondary syphilis to be recommended as the most successful at the present day are:

- 1 The continuous method of treatment as such,
- 2 The intermittent method of treatment, as carried out in Denmark or Great Britain.

<sup>63</sup> Schereschewsky, J. *Prophylax antiven* 8 220 (April) 1936.

<sup>64</sup> Millspaugh, J. A. *Prophylaxis of Venereal Disease*, U. S. Nav. M. Bull. 34 32 (Jan.) 1936.

<sup>65</sup> Mahoney, J. F. *An Experimental Resurvey of the Basic Factors Concerned in Prophylaxis in Syphilis*, Mil. Surgeon 78 351 (May) 1936.

<sup>66</sup> Martenstein, H. *Syphilis Treatment. I. Enquiry in Five Countries*, Quart. Bull. Health Organ, League of Nations 4 129 (March) 1935.

It should be specially emphasized that particularly satisfactory treatment results were also obtained in a number of clinics in the other countries, and when the methods which they use are compared, they are found to agree in striking fashion with those applied in Denmark and the United Kingdom

In making up their final recommendations the committee, composed of Jadassohn, Madsen, Harrison, Gougerot, Lomholt and Stokes, took into consideration the fact that in the systems of intermittent treatment used in Denmark and Great Britain an arsphenamine and a heavy metal are given in concurrent courses, separated by only short rest periods, so that, *in effect, the patient is receiving essentially continuous treatment by absorbing heavy metal from his intramuscular stores during the brief rest periods*. Their final conclusions follow

1 Treatment should be recommended as early as possible in the sero-negative primary stage. In this connection, the fullest possible use should be made, for purposes of diagnosis, of the microscopical examination of secretions from primary lesions or from lymph glands

2 It should be emphasized that, prior to the institution of either of the systems of treatment outlined below, there should be an adequate physical examination to determine the absence or otherwise of any indication for caution in respect of the dosage

3 It is essential that, in carrying out the treatment, a strict supervision of the patient be exercised, especially in respect of mucous membranes, skin, kidneys and liver

4 Observation, clinical and serological, after completion of treatment should be adequate and in any case for not less than three years

5 Adequate examination of the spinal fluid, at least before dismissal from observation, is essential

6 The principles to be followed in carrying out the actual treatment should be as follows

(a) To employ a comparatively heavy individual dosage of the arsenobenzene and of the bismuth or mercurial compounds, the doses being administered in comparatively rapid succession, especially at the commencement,

(b) To maintain a persistent attack on the disease, avoiding intervals of such length as to afford the parasite an opportunity of recovering,

(c) To administer approximately as much treatment to primary as to secondary cases

7 The material studied does not enable a clear decision to be made as to the relative merits of intermittent treatment with courses of injections in rapid succession separated by rest intervals of some weeks and continuous treatment or between the simultaneous employment of both arsenical and bismuth or mercury, and the system in which bismuth and mercury are withheld until a number of arsenical injections have been administered

Nevertheless, it seems practicable, from the results of the analysis and from the personal experience of the Experts, to formulate a system of intermittent treatment and one of continuous treatment, either of which can be expected to yield satisfactory results in ordinary cases of early syphilis

*It seems possible that the intermittent treatment which is suggested below may in effect be continuous, or practically continuous, treatment, owing to the continued absorption of bismuth from the sites of the injection for some weeks after any temporary suspension of the treatment*<sup>68</sup>

*The Fever Therapy of Early Syphilis*—Neymann, Lawless and Osborne<sup>69</sup> provide the latest report on the fever treatment of early syphilis. These authors treated 14 patients with early syphilis by means of from 3 to 8 bouts of fever, 7 of them also received either concurrently or immediately afterward, a short course of an arsphenamine and bismuth. All the patients who did not receive supplementary chemotherapy had a relapse, those who had this totally inadequate treatment with neoarsphenamine and bismuth have been well for periods varying from five to eighteen months.

The remainder of the recent literature on this subject has been the subject of editorial comment<sup>70</sup>

In the *Journal of the American Medical Association* issue of Dec 28, 1935, Simpson<sup>71</sup> reports the results of the treatment of early syphilis, latent Wassermann-fast syphilis, and neurosyphilis with artificial fever in combination with chemotherapeutic agents. Since the value of fever in the treatment of neurosyphilis is fully established and since the studies of the Cooperative Clinical Group have shown that the results of chemotherapeutic treatment of latent Wassermann-fast syphilis are satisfactory without fever therapy, his report is of interest mainly because of his use of fever in the treatment of twenty-six patients with early syphilis.

These twenty-six patients were treated with a total of 9 Gm of neoarsphenamine and 6 Gm of bismuth during a period of thirty weeks, supplemented by fever maintained above 105 F for thirty hours. They were followed for six to thirty months after treatment ended, and within this period of time the outcome was judged to be more satisfactory than in two control groups: one of six patients treated with fever only and the other of fourteen patients treated with thirty weeks of chemotherapy only. Simpson thought these results "to provide evidence that fever therapy may be of great value in early syphilis, particularly when chemotherapy alone appears inadequate."

In his discussion of Simpson's paper, Stokes points out that as a result of the Cooperative Clinical Group's studies we now have a highly satisfactory plan of treatment for early syphilis, which has been evaluated by the study of an unusually large group of patients. He urged that the position of this treatment plan be not jeopardized by attempts to apply a new and untried method which demands a high degree of specialization. Stokes's remarks are of sufficient importance to warrant further emphasis.

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68 The italics have been supplied by us.

69 Neymann, C A, Lawless T K, and Osborne, S L. The Treatment of Early Syphilis with Electropyrrexia, *J A M A* **107** 194 (July 18) 1936.

70 The Fever Treatment of Early Syphilis, editorial, *Am J Syph, Gonorr & Ven Dis* **20** 445 (July) 1936.

71 Simpson, W M. Artificial Fever Therapy of Syphilis, *J A M A* **105** 2132 (Dec 28) 1935.

The plan of treatment for early syphilis recommended by the Cooperative Clinical Group was not evolved suddenly from their preconceived ideas of how early syphilis should be treated but was arrived at from an extensive study and comparison of the various treatment schemes which have been proposed since the discovery of arsphenamine. The history of the development of the scheme is of interest in emphasizing this point. In 1916, seven years after the introduction of arsphenamine in the treatment of syphilis, it occurred independently to Keidel<sup>72</sup> in this country and to Almkvist<sup>73</sup> in Europe that the unsatisfactory results of the treatment of early syphilis with the arsphenamines were due to the physician's lack of a clear understanding of what he was attempting to accomplish. They felt that patients with early syphilis might be biologically "cured" if treatment was continued *without interruption* for a sufficient length of time and if, in order to avoid drug resistance, mercury was used in alternation with the arsphenamines. Almkvist decided that a year of continuous treatment was necessary, and Keidel decided upon a year of treatment after the permanent reversal of the blood Wassermann. In 1932 the Cooperative Clinical Group,<sup>74</sup> evaluating a great variety of treatment schemes for early syphilis, found that the majority of patients with early syphilis were clinically and serologically "cured" if they were given a minimum of twenty injections each of one of the arsphenamines and a heavy metal without interruption for a year during the first two years of the infection. They, therefore, accepted as satisfactory essentially the same plan proposed by Almkvist and Keidel fifteen years before.

The authority of this great amount of material followed for so long a time precludes the adoption of other treatment schemes which have a less substantial background. This is particularly true of fever therapy for two reasons.

In the first place, fever and chemotherapy in the treatment of early syphilis has been tried and found less satisfactory than other treatment plans. Malaria combined with courses of neoarsphenamine was treated about fifteen years ago and was abandoned because the immediate satisfactory results (Kyrle<sup>75</sup>) were not confirmed by subsequent developments (Kerl<sup>76</sup>). There is at present such insufficient evidence that mechanical methods for producing fever have any advantage over the older method of malaria therapy that a reopening of the question seems inadvisable.

In the second place, the proposal to use hyperpyrexia jeopardizes the advances that have already been made in the treatment of early syphilis. The knowledge

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72 Moore, J. E., and Keidel, A. The Treatment of Early Syphilis. I. A Plan of Treatment for Routine Use, *Bull. Johns Hopkins Hosp.* **39** 1, 1926. Moore, J. E., and Kemp, J. E. The Treatment of Early Syphilis. II. Clinical Results in Four Hundred and Two Patients, *ibid.* **39** 16, 1926. III. The Wassermann Reaction in Treated Early Syphilis, *ibid.* **39** 36, 1926.

73 Almkvist, J. Re Continuous Treatment of Syphilis Instead of Chronic Intermittent Treatment, *Acta dermat.-venereol.* **1** 97, 1920.

74 Stokes, J. H., Usilton, L. J., Cole, H. N., Moore, J. E., O'Leary, P. A., Wile, U. J., Parran, T., Jr., and McMullen, J. Standard Treatment Procedure in Early Syphilis. A Resume of Modern Principles, *Ven. Dis. Inform.* **15** 149, 1934. What Treatment in Early Syphilis Accomplishes, *ibid.* **15** 341, 1934.

75 Kyrle, J. Die Malariabehandlung der Syphilis, *Wien klin. Wchnschr.* **37** 1105, 1927.

76 Kerl, W. Malariabehandlung der Fruhlues, *Arch. f. Dermat. u. Syph.* **157** 294, 1929.

that the treatment of syphilis requires at least a year has gradually been accepted by a small but appreciable part of the lay population. This knowledge has been gained very gradually during the past ten years from various sources, the most important of which have been the larger syphilis clinics. It has been disseminated for the most part by patients under treatment or observation for syphilis in these clinics. However, during the last four or five years, numerous articles concerning fever therapy have appeared in the lay press. They have varied from sane accounts of the use of fever in the treatment of disease<sup>77</sup> to stories of physicians using fever to produce a sturdier crop of corn<sup>78</sup>. The layman is unable to judge the value of these articles, and, as a result, the patient with early syphilis may become the victim of the less capable or the dishonest physician. If this happens, it will not be long before both patient and physician are as confused as they were in the years immediately following the advent of the arsphenamines. The long process of reevaluation of treatment schemes and reeducation of the patient will have to be begun afresh, and in the meantime it is to be feared that the incidence of early syphilis will continue to increase.

There are many who feel that the recent recognition of syphilis as one of our major public health problems will awaken the interest of the local health officer sufficiently to secure his aid in dealing with some of the problems which have so far prevented progress in the control of the disease. This cooperation will be of value chiefly in bringing patients with early syphilis under treatment. If this can be accomplished, there is at hand a plan of treatment which, if properly executed, will give extremely satisfactory results. It is hoped that these results will not be jeopardized by any treatment schemes which, whatever their potentialities, are at the present time unproved.<sup>78a</sup>

*The Curability of Syphilis*—In regard to the attitude to be taken concerning the end-results to be achieved by modern methods of treatment, Klein<sup>79</sup> reemphasizes the caution necessary when an individual and not a group is under consideration, with particular reference to the suitability of a person with syphilis as a prospective marital partner and parent. Klein emphasizes, not too strongly, the necessity for any person with syphilis to submit to a lifetime of observation, but, in our opinion, he paints too gloomy a prospect of the eventual outcome for the marital partner and the children provided the proper follow-up regimen is observed.

#### TREATMENT-RESISTANT SYPHILIS

In a detailed review of the literature, which does not lend itself well for summary here, Beerman<sup>80</sup> points out that treatment-resistant syphilis

77 Fever as a Friend, *Scient Am* **153** 40, 1935

78 Chicago Daily News, Feb 19, 1936, p 11

78a In addition to the articles cited are numerous general discussions of the treatment of early syphilis which contain nothing new and so are not proper material for review here but which by their wide distribution in general journals have served the useful purpose of widely publicizing modern methods of treatment.

79 Klein, J. E. The Curability of Syphilis, *Arch Dermat & Syph* **33** 1055 (June) 1936

80 Beerman, H. The Problem of Treatment-Resistant Syphilis, with Special Reference to Arsphenamine-Resistant Syphilis. Review of the Literature and Experimental Study, *Am J Syph, Gonorr & Ven Dis* **20** 165 (March), 296 (May) 1936



has been variously defined but that no single definition is entirely satisfactory. He says

The essential criteria of treatment-resistant syphilis are (a) persistence of lesions, (b) persistently positive blood serologic tests and (c) persistence of spirochetes in spite of usually adequate treatment. Of these three the persistence of *Spirochaeta pallida* in the lesions is the most reliable criterion of treatment-resistance in human syphilis.

It is emphasized that resistance to treatment is a phenomenon of any stage of syphilis, but since the most characteristic lesions are cutaneous and occur in early syphilis, these have been most spoken of, and less attention has been paid to the more fundamentally important questions of visceral lesions. Beerman thinks that the classifications of resistance to treatment which previously have been suggested are meaningless.

The observations that the serologic reaction for syphilis in patients with treatment-resistant early syphilis tends to be negative or prematurely to revert to negative and that many of these patients react badly to the arsphenamines are carefully restated. In a detailed discussion of the evidence, this author concludes further that

The consensus at present seems to regard the host as the factor most responsible for treatment-resistant syphilis. While a number of studies have indicated that under certain conditions *Spirochaeta pallida* may be made to develop a certain degree of resistance to antisypilitic drugs, no one up to the present has reported the transfer of *Spirochaeta pallida* from a treatment-resistant syphilis in man to rabbits with preservation or demonstration of treatment resistant characteristics in the rabbits.

A case of treatment-resistant syphilis is reported, and the methods of therapy to be employed in such cases are discussed in detail. Finally, spirochetes from the patient were transferred to rabbits, and the disease produced was compared with that produced by the Nichols strain. In general the lesions produced by the fresh strain were less conspicuous, and larger doses of arsphenamine were required to effect a cure in rabbits than was usual with the Nichols strain.

Greenbaum and Rule<sup>81</sup> reach essentially the same conclusions from a review of the literature and report efforts to produce drug resistance in the Nichols strain of *S. pallida*. Through nine passages animals that had been given injections of the strain were treated with subcurative doses of neoarsphenamine before transfer. The animals which were infected by injection at the ninth passage were cured as readily as controls.

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<sup>81</sup> Greenbaum, S. S., and Rule, A. M. Resistant Syphilis, with Especial Reference to an Attempt to Produce Experimentally an Arsenic-Resistant (Neoarsphenamine-Resistant) Strain of *Spirochaeta Pallida*, *Pennsylvania M. J.* **39**: 339 (Feb.) 1936.

In regard to the part played by the host and the organism in the development of resistance to treatment, MacCormac<sup>82</sup> reports an instance in which both a woman and the man by whom she had been infected had treatment-resistant syphilis. This, naturally, is adduced by the author as proof that the organism is the origin of resistance to treatment.

*Serologic Resistance*—Morgan<sup>83</sup> reviews the subject of serologic resistance (so-called Wassermann fastness) and concludes that while the persistence of positive serologic reactions after treatment necessitates the making of further investigations, "in late latent syphilis treatment need not be continued on account of positive serologic reactions alone."

#### CLINICAL PHENOMENA IN EARLY SYPHILIS

*Association with Gonorrhea*—The common experience of discovering a positive reaction to the serologic test for syphilis or late lesions of the disease in a patient who can give no history of early syphilis but who has had gonorrhea has led many to assume that coexisting gonorrhea can mask the lesions of early syphilis. In this regard the report of Kemp and Shaw<sup>84</sup> is of great interest. These authors carefully examined and made follow-up serologic tests on 500 men and 500 women with acute gonorrheal urethritis. Seven men and 15 women were discovered to have primary syphilis, 6 men had noted the lesion before its discovery by the physician, and in all the patients of both sexes the nature of the lesion was clinically provable. Similarly, only 3 of 19 patients with secondary syphilis were unaware of the eruption. There were 114 other patients with latent or late syphilis at the time of admission, but follow-up serologic tests did not reveal any symptomless infection among the patients without lesions and with a negative reaction to serologic tests for syphilis when they were first seen.

*Extragenital Primary Syphilis*—In a review of the literature Wagener<sup>85</sup> discovered 7 reports of large series of patients with primary syphilis, in these the incidence of extragenital infection varied from 2.5 to 15.6 per cent. The average for the entire group was over 8 per cent. In his material 32 (11.5 per cent) chancres were extragenital,

82 MacCormac, H. Arsenic Resistant Syphilis, *Proc Roy Soc Med* **28** 1527 (Sept) 1935.

83 Morgan, A. G. The Significance of Resistant Serologic Reactions, *Ven Dis Inform* **16** 379 (Nov) 1935.

84 Kemp, J. E., and Shaw, C. The Rôle of Acute Gonorrheal Urethritis in Masking the Lesions of Early Syphilis, *Am J Syph, Gonorr & Ven Dis* **20** 56 (Jan) 1936.

85 Wagener, F. Extragenitale syphilitische Primäraffekte an der Bonner Hautklinik seit 1924, *Inaug Dissert*, Bonn, 1935.

being located as follows on the right tonsil, the upper lip and the lower lip, each in 7 instances, on the left tonsil in 4 and on the nose in 2. There was 1 instance each of primary syphilis at the corner of the mouth, on the tongue, on the eyelid, on the ring finger and about the anus. From follow-up studies the author concludes that, aside from the site of infection, no phenomena differentiated this group from other patients with early syphilis.

Tobias<sup>86</sup> provides a similar report of 65 patients with extragenital chancres and discusses at length the source of infection and the means of transmission, with the public health problems involved. The location of the lesion in this group was as follows: upper lip, 20, lower lip, 16, tonsil, 1, tongue, 6, cheek, 3, nose, 2, right index finger, 7, right middle finger, 2, breast (female), 3, breast (male), 1, scalp, 1, and chin, 3.

*Reinfection*—Because of the close medical supervision of enlisted men in the navy, Millspaugh<sup>87</sup> has the opportunity to report 7 clearly proved cases of reinfection with syphilis. Thus he does primarily to show that these seamen had achieved a biologic cure of the first infection after antisypilitic therapy, 1 with only 11 injections of neoarsphenamine and 16 of bismuth.

*Transfusion Syphilis*—Mandelbaum and Saperstein<sup>88</sup> report the development of acute gummatous osteomyelitis as the first manifestation of transfusion syphilis, eight weeks after the transfusion. This, they point out, is unique, since in all other cases reported a generalized cutaneous eruption has developed within three and a half months after the offending transfusion.

#### LATE SYPHILIS

*Treatment*—Greenbaum<sup>89</sup> reports his experience with acute late syphilis, which he defines as the eruptive stage of the second incubation period. When this stage of the disease has been reached, he believes that avoidance of therapeutic shock is sufficiently important to justify some prolongation of the patient's period of infectivity. Therefore, he advises and for several years has practiced the institution of therapy with bismuth.

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86 Tobias, N. Extragenital Chancres. A Clinical Study, *Am J Syph, Gonorr & Ven Dis* **20** 266 (May) 1936.

87 Millspaugh, J. A. Syphilitic Reinoculation, *Mil Surgeon* **79** 25 (July) 1936.

88 Mandelbaum, H., and Saperstein, A. N. Transmission of Syphilis by Blood Transfusion. A Case of Acute Gummatous Osteomyelitis, *J A M A* **106** 1051 (March 28) 1936.

89 Greenbaum, S. S. The "Bismuth Approach" in the Treatment of Acute (Late) Syphilis, *J Chemotherapy* **13** 5 (April) 1936.

*Syphilis of the Bladder*—In a search of the literature since 1900 Finestone<sup>90</sup> discovered reports of 158 cases of syphilis of the bladder, which he analyzes in detail. He concludes

There is marked laxity in the reporting of cases which are neither thoroughly studied nor followed and adequately controlled.

Only eight investigators have subjected the lesions to microscopic study. Only one shows typical histopathology. Two are claimed to have shown specific histopathology but are not reported in detail. The five others give descriptions of nonspecific inflammation.

Not one of the cases described measures up to the standard set by Young, who maintains that the spirochaeta must be demonstrated in the lesions.

To this he adds his own experience in 2 cases. One was typical of the group in which the diagnosis rests on the therapeutic test, the other apparently was typical of the same group, but later it was discovered that the patient had a tuberculous kidney, and the vesical lesion was thought to have been secondary to it.

In addition to the type of lesions with which Finestone was concerned, Kasztriner<sup>91</sup> reports on a series of patients with lesions of early syphilis who had symptoms of acute cystitis and in whom cystoscopic examination revealed erythematous syphilds, papules and ulcers. Because of the coexistence of cutaneous lesions and the prompt relief following treatment, this author believes the lesions represented early syphilis of the bladder, despite the fact that *S. pallida* could not be found. Kâmil<sup>92</sup> reports a similar case.

*Syphilis of the Lung*—Takei<sup>93</sup> reports the case of a 48 year old Japanese laborer who was observed during an acute illness, which was characterized by pain in the right side of the chest, fever and productive cough. Because of the fact that he had syphilis and cutaneous gummas, that no tubercle or other bacilli or fungi could be found in the sputum and that antisyphilitic therapy was followed by critical defervescence, it was suggested that he had syphilis of the lung. Curious as to the validity of the diagnosis, the author collected reports of 95 cases from the literature in which the diagnosis of pulmonary syphilis had been based on the same criteria as his own and analyzed them for features in common. The ages of the patients varied widely, but most of them were in from the third to the sixth decade of life, and the average duration of syphilis had been eighteen years. There were two and three-tenths times as many men as women. In two thirds of the patients

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90 Finestone, E. O. Syphilis of the Bladder, Surg, Gynec & Obst **62** 93 (Jan.) 1936.

91 Kasztriner, I. Syphilis of the Bladder, Ztschr f urol Chir **41** 477 (Feb. 12) 1936, abstr, Ven Dis Inform **17** 217 (July) 1936.

92 Kâmil, F. Blasenlues, Ztschr f Urol **29** 163, 1935.

93 Takei, U. Ueber Lungensyphilis, J Orient Med **24** 10 (Jan.) 1936.

the lesion was in the right lung only, in a sixth each it was in the left lung or was bilateral. In only 3 per cent was the process at the apex of the lung. Complicating lesions of syphilis were present in the bones, heart, aorta, spleen and liver. The mortality rate was 34.7 per cent in the group of cases reported in the literature, but the author thinks that the prognosis is good if antisyphilitic therapy is given early.

*Syphilis of the Stomach*—Pusch<sup>94</sup> studied 35 cases which had been reported in the literature as instances of syphilis of the stomach and discusses them in detail. Clinically, the differential diagnosis lay between syphilis of the stomach and cancer, and usually it had been impossible to reach a decision since the salient symptoms and findings are alike in the two conditions. It may be helpful, however, that syphilis of the stomach commonly occurs before the age of 40. This is not a dependable feature, however, and since neither serologic tests for syphilis nor an apparent response or lack of response to treatment should be relied on, operation should not be delayed for a therapeutic test, thereby running the risk of depriving a patient with an operable carcinoma of the benefits of surgical treatment. Even in syphilis of the stomach, operation is frequently necessary to relieve obstruction caused by scarring.

Williams<sup>95</sup> objects to the requirement that a lesion of the stomach may not be considered due to syphilis unless animal inoculation proves the presence of *S. pallida*. Such a requirement, he says, is not met in the diagnosis of other lesions of late syphilis. The diagnosis of gastrointestinal syphilis may be made, in his opinion, if the following criteria are fulfilled:

- 1 Roentgenologic evidence of smooth, tubelike gastric deformity
- 2 Youth of the patient
- 3 The presence of other evidences of syphilis
- 4 Improvement under antisyphilitic treatment
- 5 If an operation is performed, the discovery of an inflammatory mass
- 6 The demonstration in excised tissue of lesions compatible with syphilitic inflammatory tissue

#### CARDIOVASCULAR SYPHILIS

*Unusual Findings*—Richter<sup>96</sup> reports the first recorded instance of the demonstration of *S. pallida* in an aortic cusp. The patient had also

94 Pusch, L. C. Syphilis of the Stomach. A Review of Thirty-Five Selected Cases, *Internat. Clin.* **1**: 56 (March) 1935.

95 Williams, C. The Diagnosis of Syphilis of the Gastro-Intestinal Tract, *Virginia M. Monthly* **62**: 322 (Sept.) 1935.

96 Richter, A. B. Treponema Pallidum in Syphilitic Aortic Valvulitis of a Congenitally Bicuspid Valve with Subaortic Stenosis. Report of a Case, *Am. J. Path.* **12**: 129 (Jan.) 1936.

congenital heart disease Blackman<sup>97</sup> adds 2 cases to the solitary case previously reported of syphilis of the mitral valve and the membranous interventricular septum, both patients had syphilitic aortitis, with the typical anatomic picture of aortic insufficiency, and the process which involved the septum and the mitral valve was a direct continuation of the process in the root of the aorta, so it chiefly involved the anterior mitral segment Sohval<sup>98</sup> describes 2 cases of gumma of the heart and reviews the 97 previously reported cases The most frequent site for gumma of the heart is in the myocardium of the left ventricle, particularly at the base of the interventricular septum In this location the process may interfere with the conduction system, and heart block may supervene The diagnosis is seldom made clinically but should be suspected, according to Sohval, in the presence of "unusually situated, weird stenotic murmurs, unexplained roentgen shadows at the cardiac margins and heart block in a patient in whom syphilis is suspected"

*Syphilitic Aortitis in the Young*—In a review of the literature Norris<sup>99</sup> could find reports of only 12 cases of syphilitic aortitis in which the syphilitic infection could be either proved or reasonably assumed to be of congenital origin To this experience he adds a report of 2 patients, a girl of 9 and a boy of 17, both of whom died suddenly and were found at autopsy to have typical syphilitic aortitis Congenital syphilis was not proved in either instance, but in both it seemed most probable In his discussion, Norris brings out that, since the precocious development of syphilitic aortitis only a few years after infection is acquired is well known, it cannot be said that such was not the case here, since congenital syphilis was not proved, but he is of the opinion that the assumption of the congenital nature of the infection is justified

*Syphilitic Myocarditis*—Magill<sup>100</sup> reports on a series of patients who presented a picture which he considers to be typical of syphilitic myocarditis All were young (the oldest was 46), and all were suffering from moderate to severe degrees of cardiac decompensation unexplained by any of the usually accepted causes of cardiac disease Aside from cardiac enlargement and the usual presence of a protodiastolic gallop rhythm, the examination of these patients revealed singularly little

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97 Blackman, S S, Jr Syphilis of the Mitral Valve and the Membranous Interventricular Septum of the Heart, Bull Johns Hopkins Hosp **57** 111 (Sept) 1935

98 Sohval, A R Gumma of the Heart Report of Two Cases, Arch Path **20** 429 (Sept) 1935

99 Norris, R F Syphilitic Aortitis in Childhood and Youth Report of Two Cases with Sudden Death, Bull Johns Hopkins Hosp **57** 206 (Oct) 1935

100 Magill, T P Syphilitic Myocarditis, Bull Johns Hopkins Hosp **57** 22 (July) 1935

There was no arteriosclerosis, and the blood pressure was not elevated, but in most of them the pulse pressure was low, and there were no signs of organic valvular disease. All of these patients either showed a positive reaction to serologic tests for syphilis or gave a history of precedent antisyphilitic treatment.

Five came to autopsy, in none was there disease of the coronary arteries, but all manifested a uniform pathologic picture characterized microscopically by extensive scarring and round cell infiltration of the myocardium.

*Abdominal Aneurysm*—Kampmeier<sup>101</sup> describes the clinical findings in 73 cases in which a diagnosis of abdominal aneurysm was made and the anatomic findings in the 38 that came to autopsy. Death was due to rupture of the aneurysm in 31 of these 38 patients. Pain was the most common symptom, varying in type but being rather uniformly severe. The clinical findings were variable, but a palpable tumor was found in 42 of the 73 patients, and roentgenograms revealed erosion of the vertebrae in 18 of the 24 so studied. Two thirds of the patients were under 45. The majority were Negro men who did hard labor and 39 were proved to have syphilis.

*The Incidence of Cardiovascular Syphilis*—Sprague and White,<sup>102</sup> in a general consideration of the prophylaxis of heart disease, forecast that syphilitic heart disease may soon be wiped out by virtue of the adequate treatment of early syphilis, and in this connection present some extremely interesting figures. In the ten years from 1900 through 1909 aortic aneurysm was the diagnosis for 113 of the 51,875 patients admitted to the Massachusetts General Hospital, an incidence of approximately 0.2 per cent. In the decade which ended in 1934, however, in spite of better methods of diagnosis, the diagnosis of aortic aneurysm was made for only 61 of the 75,184 patients admitted, an incidence of 0.08 per cent.

Mahei, Sittler and Elliott<sup>103</sup> analyzed the data on 1,000 private patients with heart disease, all living in the vicinity of Chicago. In 97, or 9.7 per cent, the heart disease was due to syphilis.

*General Considerations*—In an important communication Cormia<sup>104</sup> reports a review of all of the cases of cardiovascular syphilis in which

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101 Kampmeier, R. H. Aneurysm of the Abdominal Aorta. A Study of Seventy-Three Cases, *Am J M Sc* **192** 97 (July) 1936.

102 Sprague, H. B., and White, P. D. The Etiology of Heart Disease with Special Reference to the Present Status of the Prevention of Heart Disease, *J A M A* **105** 1391 (Nov. 2) 1935.

103 Maher, C. C., Sittler, W. W., and Elliott, R. A. Heart Disease in the Chicago Area, *J A M A* **105** 263 (July 27) 1935.

104 Cormia, F. E. Cardiovascular Syphilis. A Necropsy Survey, *Canad M A J* **33** 613 (Dec.) 1935.

autopsy was performed in the Royal Victoria Hospital in the thirty-five years ending in 1934. There were 199 such cases, representing 2.68 per cent of the total number of autopsies. By a tabulation of incidence for five year periods the author shows that aside from a peak in the period 1910 to 1914, the incidence of cardiovascular syphilis has not materially changed but the incidence of myocarditis and that of coronary artery disease are increasing. Not one of these patients had had adequate treatment for early syphilis.

There were 156 men and 43 women. The common age of death was 50 years. Fifty-eight patients had other lesions of syphilis, in these cardiovascular syphilis was the cause of death in all but 6, 3 of whom had dementia paralytica and 1 had tabes dorsalis. In 34 of the 44 instances of aortitis there had been no symptoms, which is not surprising, since all of those with outspoken dilatation of the aorta were considered as having fusiform aneurysm. The 10 with symptoms had lived on the average only a year and two months after the symptoms developed. The span of life from the development of symptoms until death had been three years for patients with aneurysm, one year and ten months for those with aortic regurgitation and two years for those with both conditions. There were 35 instances of syphilitic involvement of the coronary arteries, either at their ostia or in the distal trunks, one third of the 33 patients with aortic regurgitation and 18 of the 40 with both aortic regurgitation and aneurysm manifested this abnormality. However, only 1 of the 60 patients with aneurysm alone also had syphilitic disease of the coronary arteries, although in 18 arteriosclerotic changes were noted. There were 20 patients in whom syphilis of the myocardium independent of coronary disease was suspected, it seemed definite in 14 and questionable in 6.

Bourne,<sup>105</sup> in a general consideration of cardiac pain, says

Patients with aortic syphilis suffer from three types of pain, excluding that produced by a definite aneurysm—these are angina of effort, spasmodic angina, and nocturnal pain. The angina of effort is identical in every particular with that already described, but it is found typically in a patient who has no signs of hypertrophy or arteriosclerosis, and in whom, if there is no aortic incompetence, the heart is not enlarged. In patients with a syphilitic aortic regurgitation, in addition to angina of effort, a spasmodic angina is sometimes found. This is symptomatically identical with spasmodic angina in nonsyphilitic cases. A nocturnal pain, recognized sometimes by the patients as being of a cardiac nature, is not uncommon in syphilitic aortitis. It is generally central, and may be felt in front under the sternum, or may be referred more to the back.

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<sup>105</sup> Bourne, G. The Symptomatology of Cardiac Pain, *Brit. M. J.* **1** 1109 (June 1) 1935.



*The Treatment of Cardiovascular Syphilis*—Employing the method of study used by Moore, Danglade and Reisinger,<sup>106</sup> Stratton<sup>107</sup> studied the effects of treatment or its lack on the life span of 80 patients with aortic insufficiency or aneurysm and corroborated in every respect the earlier observations Cole and Usilton,<sup>108</sup> writing for the Cooperative Clinical group, present a series of three papers which are based on a study of the material collected and analyzed by the group

Padget and Moore<sup>109</sup> seized the opportunity to resurvey the group of patients reported on by Moore, Danglade and Reisinger<sup>106</sup> after an additional three years of observation. Using a simpler method of analysis than in the previous study and dealing only with the duration of life in reference to antisyphilitic treatment, these authors consider a group of 161 cases of aortic regurgitation or saccular aortic aneurysm in which the mean potential period of observation was ten and three-fourth years and in which no living patient had been under observation for less than five and one-half years. One third of the patients had died in less than a year of observation and so were eliminated from a consideration of the therapeutic results.

Such a study is not complete, say the authors, until all the patients are dead, but in the meantime examination of the mortality rates for various groups affords valuable information. "The mortality rate for the poorly treated group was 1.37 times that of the well treated group in patients with aneurysm, 2.52 times as great in those with aortic insufficiency, and 2.02 times as great for the group as a whole," with an even more striking contrast when deaths due to cardiovascular syphilis and deaths due to other diseases or to causes unknown are considered. In the 70 patients of the group considered who are dead "the duration of life from onset of symptoms was 1.7 times as great in the well treated as in the poorly treated patients for the whole group, 1.71 times as great in those with aneurysm, and 1.37 times as great in the patients with aortic insufficiency." The latter figure was not claimed to have certain statistical significance, but all others were

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106 Moore, J. E., Danglade, J. H., and Reisinger, J. E. *The Treatment of Cardiovascular Syphilis*, Arch Int Med **49** 879 (June) 1932.

107 Stratton, E. K. *The Treatment of Cardiovascular Syphilis. A Study of the Duration of Life in Eighty Treated and Untreated Patients with Aortic Aneurysm and Aortic Regurgitation*, Arch Int Med **56** 773 (Oct.) 1935.

108 Cole, H. N., and Usilton, L. J. *Cooperative Clinical Studies in the Treatment of Syphilis. Cardiovascular Syphilis, I. Uncomplicated Syphilitic Aortitis. Its Symptomatology, Diagnosis, Progression and Treatment*, Arch Int Med **57** 893 (May) 1936, II *Syphilitic Aortic Regurgitation. Its Treatment and Outcome*, *ibid* **57** 910 (May) 1936, III *Aneurysm. Its Symptomatology, Diagnosis, Treatment and Outcome*, *ibid* **57** 919 (May) 1936.

109 Padget, P., and Moore, J. E. *The Results of Treatment in Cardiovascular Syphilis. A Report of Three Years' Additional Observation*, Am Heart J **10** 1017 (Dec.) 1935.

The authors conclude that "properly directed antisyphilitic therapy results in a prolongation of life in two thirds of the patients with saccular aortic aneurysm or syphilitic aortic insufficiency. The remaining third come under observation with an initially bad prognosis, and do not survive sufficiently long for proper therapy to be administered."

#### NEUROSYPHILIS

*Statistics*—Merriman<sup>110</sup> estimates that neurosyphilis occasioned 11.3 per cent of all admissions to civil state hospitals during the year ending in June 1933, and he restates the estimate that neurosyphilis cost the state of New York alone \$13,500,000 during the year 1931.

In an analysis of the outcome in patients with dementia paralytica Derby<sup>111</sup> reports on 1,475 consecutive admissions to a state hospital during the fifteen year period from 1917 to 1931. Malaria therapy was adopted in 1924 and tryparsamide the following year. A contrast is presented. The patients who received no treatment lived for an average of one and a third years after admission to the hospital, those who were treated by all means other than malaria lived for just more than three years, but the average survival of the patients who received chemotherapy and malaria treatment was five and three-fourth years.

*The Genesis of Neurosyphilis*—In a lengthy review of the evidence regarding habitus and constitutional make-up as factors influencing the development of neurosyphilis, Meggendorfer<sup>112</sup> concludes that he agrees with most writers since Paracelsus that in a given subject infection with syphilis takes a form which is determined by the host but that there is as yet no evidence from which to determine the constitutional factors that are responsible.

Kemp and Menninger,<sup>113</sup> in examining the records of 1,500 patients admitted consecutively to a syphilis clinic, found 265 patients with neurosyphilis in whom the duration of infection and the amount of treatment for early syphilis could be accurately determined. From an analysis of this material they conclude that inadequate treatment for early syphilis does not increase the later incidence of neurosyphilis but does operate materially to shorten the incubation period. A similar conclusion is reported by Hall<sup>114</sup>.

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110 Merriman, W. E. Syphilis and Mental Disease, *J. Social Hyg.* **21** 164 (April) 1935.

111 Derby, I. M. Life Expectancy in General Paresis, *Psychiatric Quart.* **9** 458 (July) 1935.

112 Meggendorfer, F. Die Rolle der Konstitution bei der Spätlues des Nervensystems, *Deutsche Ztschr. f. Nervenheilk.* **139** 157 and 191, 1936.

113 Kemp, J. E., and Menninger, W. C. The Influence of Inadequate Treatment of Early Syphilis on the Incidence and Incubation Period of Neurosyphilis, *Bull. Johns Hopkins Hosp.* **58** 24 (Jan.) 1936.

114 Hall, T. B. The Influence of Early Therapy on the Incubation Period of Syphilis, *South M. J.* **28** 631 (July) 1935.

Beinger<sup>115</sup> comments on the Russian-German expedition to Buriat-Mongolia. In this isolated Soviet republic the incidence of syphilis is high (25 to 50 per cent), and the disease is not treated. This expedition was organized to determine the form which syphilis takes when not influenced by treatment. Unfortunately, conditions were such that careful statistical surveys could not be made, but, according to this author, neurosyphilis was found to have approximately the same incidence as in European countries, indicating that neither a primitive racial stock nor the absence of antisyphilitic treatment protects against its development.

*Disturbance of Carbohydrate Metabolism in Neurosyphilis*—There were many suggestions in the earlier literature that syphilis was an important cause of diabetes, and in the recent past all investigators have recognized the fact that since syphilis and diabetes are both not uncommon diseases their coexistence should be expected. Properly directed studies have shown that there is no evidence to indicate that the development of clinically typical diabetes mellitus in a patient with syphilis necessitates the assumption of an etiologic relationship. Blackford and Venable,<sup>116</sup> however, describe 2 patients, neither of whom was completely studied, but in both of whom glycosuria appeared only during convulsions associated with "paretic neurosyphilis." The authors suggest that the glycosuria may have resulted from syphilitic disease of the basal nuclei and not from true diabetes. Schube,<sup>117</sup> reasoning that since the lesions of parenchymatous neurosyphilis are widely distributed throughout the nervous system, a *piqûre* phenomenon might sometimes occur, examined the level of the blood sugar during fasting in 211 patients with various forms of neurosyphilis, with negative results.

*The Treatment of Neurosyphilis*—Although Lorenz<sup>118</sup> begins a general discussion of the treatment of neurosyphilis with the statement that "the treatment of neurosyphilis is largely a problem for the general practitioner," such is not the usual opinion, and the treatment of neurosyphilis in most part remains properly concentrated in the hands of the experienced few. Except for one paper on the use of acetarsone in the therapy of neurosyphilis, recent contributions to the subject have dealt entirely with induced fever. Here, authors have discussed the

115 Beringer, K. Die syphilitischen Erkrankungen des Nervensystems bei den Burjato-Mongolen, Arch f Psychiat **103** 359, 1935.

116 Blackford, L. M., and Venable, J. H. Hyperglycemia and Paresis, New England J Med **214** 140 (Jan 23) 1936.

117 Schube, P. G. The Blood Sugar in Uncomplicated and Untreated Neurosyphilis, J Lab & Clin Med **21** 404 (Jan) 1936.

118 Lorenz, W. F. The Treatment of Neurosyphilis, South M J **29** 74 (Jan) 1936.

indications for fever therapy, the choice of method, complications to be feared, the mode of action and the results to be obtained

*Acetarsone in the Treatment of Neurosyphilis*—Sezary and Barbé<sup>119</sup> report that they have used acetarsone for the treatment of dementia paralytica since 1921 with “cure,”<sup>120</sup> improvement, arrest and failure, respectively, in one fourth of their patients. Unfortunately, the number of patients they have so treated is not stated.

*Indications for Fever Therapy*—Menzies<sup>121</sup> emphasizes that fever therapy should not be limited to patients with dementia paralytica but that patients with other forms of neurosyphilis, especially those with tabes dorsalis, may be much benefited by it. The pains of tabes, he says, respond particularly well to fever therapy, although, of course, some disability usually persists.

Doan and Hargraves<sup>122</sup> approach the question from the point of view of the cellular pathologist. It is impossible, they say, rationally to determine the uses and limitations of fever therapy until the fundamental mechanism which underlies each disease process has been discovered, the influence of fever on the various physiologic and pathologic functions of the body has been established and the effect of the latter on the former has been carefully calculated.

*The Choice of Method for Fever Therapy*—With the great popularization of mechanical methods of elevating the temperature of the human body, there has been a rather generalized, often thoughtless rush to utilize these methods for the treatment of neurosyphilis. The results of the experiences previously summarized<sup>1</sup> seemed to indicate the superiority of malaria for the treatment of neurosyphilis, but comparisons of strictly parallel series were lacking. Epstein, Solomon and Kopp<sup>123</sup> now supply that defect. From a careful survey of the literature and a comparison of the results which they obtained by the diathermy fever treatment of 33 patients with the outcome observed in a similar group they had treated with malaria, these authors conclude: “In our hands, fever produced by diathermy has some value in the treatment of dementia paralytica but it is not so good as malaria therapy. Likewise, in a review of the literature it fails to prove to be a valuable substitute for malaria, although from our studies it appears to have distinct therapeutic value.”

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119 Sezary, A., and Barbe, A. The Treatment of General Paresis with Stovarsol, *Internat Clin* **1** 130 (March) 1936.

120 The quotation marks are ours.

121 Menzies, E. C. Rationale of Malarial Therapy in Cerebrospinal Syphilis, *Canad M A J* **33** 504 (Nov.) 1935.

122 Doan, C. A., and Hargraves, M. M. Fever Therapy. Its Indications and Its Limitations, *Hospitals* **10** 88 (June) 1936.

123 Epstein, S. H., Solomon, H. C., and Kopp, I. Dementia Paralytica. Results of Treatment with Diathermy Fever, *J A M A* **106** 1527 (May 2) 1936.

Desjardins,<sup>124</sup> while recommending that mechanically induced fever should supplant malaria for reasons of safety and convenience, says

These tests appear to have shown that in dementia paralytica, tabes dorsalis and syphilis of the nervous system generally, the results obtained by physical methods appear to be about the same as those obtained by malarial inoculation

He adds, however

The evidence is not absolutely conclusive because the number of patients is not yet sufficiently large                      our own experience                      has been too limited

In the selection of the physical method to be employed, Desjardins, Stuhler and Popp<sup>125</sup> note the tendency to employ the "hot box" rather than electrical methods for the elevation of body temperature and describe in detail the Kettering hypertherm, which is an excellent example of this type of apparatus

In almost all the treatment of neurosyphilis with malaria the tertian variety has been used, and in all the large series of cases in the literature this variety has been employed. It has been common experience, however, that many Negroes are spontaneously immune to tertian malaria, and in several centers it has become the practice regularly to treat patients of this race with quartan malaria, without, however, there being indisputable evidence that the end-results were as good. This needed evidence is now slowly accumulating, and Branche<sup>126</sup> reports on a series of 36 Negroes with dementia paralytica treated with quartan malaria in which the primary clinical results were excellent, his report was made too soon after the treatment was given to allow an evaluation of the final results. An interesting, although probably not practicable, suggestion is made by van Rooyen and Pile,<sup>127</sup> who treated 12 patients with dementia paralytica with ape malaria (*Plasmodium Knowlesi*), with apparent good results.

*Untoward Results from Therapeutic Malaria*—Shaughnessy<sup>128</sup> notes that although Great Britain and Denmark have regulations which require that a patient be screened during the course of inoculation malaria, no such regulations exist in the United States. In his opinion this is reprehensible, because to him the evidence is imperfect that the sexual

124 Desjardins, A. U. Fever Therapy, *Arch Phys Therapy* **17** 206 (April) 1936

125 Desjardins, A. U., Stuhler, L. G., and Popp, W. C. Fever Therapy for Gonococcal Infections. II, *J. A. M. A.* **106** 690 (Feb. 29) 1936

126 Branche, G. C. Therapeutic Quartan Malaria in the Treatment of Neurosyphilis Among Negroes, *J. Nerv. & Ment. Dis.* **83** 177 (Feb.) 1936

127 van Rooyen, C. E., and Pile, G. R. Observations on Infection by *Plasmodium Knowlesi* (Ape Malaria) in the Treatment of General Paralysis of the Insane, *Brit. M. J.* **2** 662 (Oct. 12) 1935

128 Shaughnessy, H. J. Artificially Induced Malaria as a Public Health Hazard, *Illinois M. J.* **69** 147 (Feb.) 1936

cycle of the parasite, and therefore the transmissibility of the disease by mosquitoes, disappears on repeated man to man passage. In support of this view he mentions a group of 11 patients, 6 hospital employees and 2 nearby residents in whom atypical malaria developed while the treatment of patients with malaria inoculata was being carried on in the hospital. Unfortunately for the substantiation of his contention, it is possible that the strain of therapeutic malaria employed had been freshly isolated.

Petersen<sup>129</sup> reports that in 14 of 261 patients who were treated with tertian malaria the parasite was found in the blood as long as one hundred and fifty weeks after the cessation of fever and after the patients had received an average of 44 Gm of quinine. Nine other patients and 2 patients seen after malaria therapy had been given elsewhere, representing infection with four different strains of *Plasmodium vivax*, suffered definite clinical relapse. The author does not comment on whether the strains were freshly isolated or not or whether it is possible that the drug used in the treatment of the original infection might have been substandard.

Milbradt<sup>130</sup> saw no serious damage to the liver develop in over 1,000 cases of inoculation malaria. There was no swelling of the liver except when icterus was present and seldom then. In 25 cases tests of hepatic function were made before and after treatment with malaria and in the few patients in whom some damage was detected immediately after the fever was terminated the results of later tests were within the normal range.

*The Mode of Action of Malaria*—Wagner-Jauregg<sup>131</sup> reviews the available evidence and concludes that malaria is superior to other means of inducing fever for the treatment of neurosyphilis.

The mode of action of fever on the nervous system has been, he says, the subject of much speculation, few facts have been obtained. Hypotheses have been advanced attempting to explain the observed facts on the basis of some change wrought in the reticulo-endothelial system by fever, by assuming a change from an anergic to an allergic state or an increase in the "reactivity" of the body, and by assigning a fundamental causal relationship to the observed increase in the opsonic index and the greater rate of antibody formation. These and other speculations may be true or partly so, but there is evidence that direct action occurs within the nervous system, there are characteristic changes

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129 Petersen, M. C. Recurrence of Inoculation Malaria, *J. A. M. A.* **106** 775 (March 7) 1936.

130 Milbradt, W. Zur Frage der Leberschädigung nach Impfmalaria, *Dermat. Wchnschr.* **101** 1182 (Sept. 21) 1935.

131 Wagner-Jauregg, J. Fever Therapy. Its Rationale in Diseases of the Nervous System, *Edinburgh M. J.* **43** 1 (Jan.) 1936.

in the cerebrospinal fluid during malaria, anatomic evidence of focal reaction is repeatedly observed, and patients with "preparetic neurosyphilis" frequently show psychic disturbances while undergoing treatment with malaria. Doan and Hargraves<sup>122</sup> report observations on the blood picture and cellular reactions of man and rabbits during induced fever but are as yet unable to interpret their findings in terms of fundamental cellular reaction. Paulian and Tanasescu<sup>132</sup> believe the fundamental beneficence of malaria is the alteration of the hemato-encephalic barrier so as to allow greater penetration of the neuraxis by treatment given after the fever has been induced. In supporting this contention they state that whereas normally the trivalent arsenicals penetrate to the cerebrospinal fluid only in traces, in patients who are given malaria treatment there may be as much as 2 mg of arsenic per liter of cerebrospinal fluid four hours after the injection of 0.3 Gm of neoarsphenamine.

*The Results of Treatment of Neurosyphilis*—In an article of extreme interest and great value Cheney<sup>133</sup> analyzes the data relating to 5,229 patients with dementia paralytica who were treated in the hospitals of the New York State Department of Mental Hygiene. Two hundred and forty-nine patients were treated with tryparsamide, 20 per cent of these gained a full remission and an additional 25 per cent were improved. There were 410 patients treated with malaria alone or in conjunction only with a trivalent arsenical and heavy metal, 18 per cent of these gained a full remission, and an additional 32 per cent were improved. Finally, 2,507 patients received, in addition to other therapy, both malaria and tryparsamide, 17 per cent of these gained remission, and an additional 38 per cent were improved. Only 15 per cent of the group treated by both methods have died, however, while 31 per cent of those treated with tryparsamide alone and 29 per cent of those who received only malarial therapy are dead. The combined therapy, then, is followed by no more complete remissions than either method alone. It is, however, followed by a somewhat higher percentage of improvement than either malaria or tryparsamide alone but allows to survive, unimproved, twice as many patients as either of the other methods of therapy. Levin<sup>134</sup> treated 100 patients with dementia paralytica with malaria alone and a similar

132 Paulian, D., and Tanasescu, G. Recherches sur la permeabilite aux novarsenobenzols de la barriere hemato-meningo-encephalitique dans la paralysie generale avant et apres la malaritherapie, Bull Acad de med, Paris **113** 850 (June 11) 1935.

133 Cheney, C. O. Clinical Data on General Paresis, Psychiatric Quart **9** 467 (July) 1935.

134 Levin, H. L. Treatment of General Paresis. Comparative Results, Psychiatric Quart **9** 636 (Oct) 1935.

group with malaria followed by tryparsamide. He found exactly the same state of affairs as did Cheney in the patients who had only one or two courses of tryparsamide after malaria treatment but discovered that the incidence of improvement was greatly increased by prolonging the tryparsamide treatment to 30 or 40 or more injections.

Solomon and Epstein<sup>135</sup> present a small series of cases the study of which suggests that therapy with both malaria and tryparsamide is more effective if the malaria is preceded by a considerable number of injections of tryparsamide.

Ridgway<sup>136</sup> and Buduls<sup>137</sup> report on a series of malaria-treated patients with dementia paralytica in which the results were in keeping with previous experiences.<sup>1</sup>

*The Fever Therapy of Ocular Syphilis*—Clark<sup>138</sup> presents a most encouraging report of the results of treatment by fever therapy of 12 patients with advanced primary atrophy of the optic nerve. Inoculation with malaria, which he considers superior to other methods, was employed for all but 1 patient (she was refractory to inoculation). Four gained no benefit, and the process advanced to the stage of complete blindness, but in 8 the process was arrested, and some gained a little improvement in visual acuity or the defects in the visual fields were reduced.

Culler and Simpson,<sup>139</sup> in a bizarre grouping of syphilitic conditions about the eye which are unrelated in their pathogenesis, discuss the results which were obtained by a total of fifty hours of fever with temperatures above 105° F induced in a Kettering hypertherm. Four patients with extra-ocular palsy were not improved, but 11 patients with previously refractory or relapsing interstitial keratitis were improved, and in 10 patients with exudative uveitis resolution was dramatically prompt and complete. In 14 patients with optic neuritis or neuroretinitis and in 7 with choroiditis the acute process subsided after fever therapy, but there were the expected residua. Sixteen patients with (presumably primary) atrophy of the optic nerve were so treated. It is reported that no change was obtained, but it is not possible from the report to determine whether atrophy continued or whether the progress of the process was stopped.

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135 Solomon, H. C., and Epstein, S. H. General Paresis. Treatment by Tryparsamide-Induced Fever Sequence, *Am J Syph, Gonorr & Ven Dis* **20** 281 (May) 1936.

136 Ridgway, R. F. L. Malaria Treatment of Paresis, *Pennsylvania M J* **39** 329 (Feb.) 1936.

137 Buduls, H. *Allg Ztschr f Psychiat* **104** 168 (Feb. 3) 1936.

138 Clark, C. P. Rôle of Malaria in Control of Atrophy of the Optic Nerve Due to Syphilis, *Arch Ophth* **15** 250 (Feb.) 1936.

139 Culler, A. M., and Simpson, W. M. Artificial Fever Therapy in Cases of Ocular Syphilis, *Arch Ophth* **15** 624 (April) 1936.



*Clinical Phenomena of Neurosyphilis*—A group headed by Langworthy<sup>140</sup> has been systematically studying the tone and function of the bladder and the pathways involved in their control in man and in experimental animals. For this purpose they have developed a technic for kymographic recording of the response of the bladder to successively introduced increments of fluid (in man usually 50 cc). Records so obtained graphically present evidence of the conditions of vesical dynamics. They emphasize that changes observed are due to the anatomic location of a lesion in the central nervous system and not to its etiology. Tabes dorsalis, other diseases which involve the posterior roots, experimental section of the second, third and fourth posterior sacral roots and lesions of certain cerebellar pathways produce similar pictures. The bladder has a large capacity, a low resting pressure and poor power as measured by the height to which pressure may be elevated and sustained by a voluntary effort to micturate. It shows little response to stretching and few or no spontaneous contractions. These abnormalities "are dependent on a loss of perception of bladder distention due to injury of the sensory nerve fibers—made worse by the stretching of the wall." Their review of the histories of 278 patients with tabes dorsalis revealed that 140 of them had complained of urinary symptoms. Incontinence, which was nocturnal in 22, was noted in 83 cases, 71 patients had experienced hesitancy, and 19 had suffered from acute urinary retention. Almost all the group had had lightning pains at some time, but vesical crises were infrequent.

Binet and Parrot<sup>141</sup> emphasize that in patients suffering the constant vomiting of tabetic gastric crises, the loss of chlorides may soon overshadow other elements in the pathogenesis of the clinical condition, and proper therapy includes replacement of the lost chlorides when necessary.

While we have found it necessary to eliminate from consideration here discussions of small series or individual case reports which relate to treatment or the well recognized reactions therefrom, we have encountered a few descriptions of unusual clinical conditions produced or probably produced by syphilis which we think should be mentioned.

Uchimura and Akimoto<sup>142</sup> present the case of a Japanese housewife with syphilis in whom pseudohypertrophic muscular dystrophy and a

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140 Dees, J. E., and Langworthy, O. R. Experimental Study of Bladder Disturbances Analogous to Those of Tabes Dorsalis, *J. Urol.* **34** 359 (Nov.) 1935. Langworthy, O. R., Lewis, L. G., Dees, J. E., and Hesser, F. H. Clinical Study of the Control of the Bladder by the Central Nervous System, *Bull. Johns Hopkins Hosp.* **58** 89 (Feb.) 1936.

141 Binet, L., and Parrot, J. La crise gastrique du tabes, crise hypochloremiante, *Presse med.* **43** 2001 (Dec. 11) 1935.

142 Uchimura, Y., and Akimoto, H. Ueber die Wernickesche Poliomyelitis als Teilerkrankung der vascularen Hirnlnes, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **152** 685 (May) 1935.

nondescript psychosis of the manic type developed. The complement fixation test of the cerebrospinal fluid gave a negative reaction, but there was an excess of globulin, and the colloidal curve was abnormal. Death ensued, and necropsy revealed extensive (supposedly syphilitic) endarteritis, which had produced in the brain and brain stem changes similar to those described as Wernicke's polioencephalitis.

Karnosh and Connor<sup>143</sup> discuss the infrequency with which neurosyphilis attacks the basal nuclei and point out that pseudobulbar palsy with pathologic grimacing as a result of neurosyphilis is rare. They have observed 2 cases, however, which are reported in full.

Winkelman<sup>144</sup> in a monographic series of articles gives a detailed discussion of syphilis of the spinal cord, with a complete bibliography. The article does not lend itself to summary here.

#### THE RELATIONSHIP BETWEEN SYPHILIS AND OTHER DISEASES

*Syphilis and Tuberculosis*—Guild and Nelson<sup>145</sup> investigated current practice in the diagnosis and treatment of coexistent syphilis and tuberculosis by sending questionnaires to representative tuberculosis sanatoriums. Replies were received from 67, representing experience with more than 25,000 patients with tuberculosis during 1933. It was found that the hospitals in which a serologic test for syphilis was made only on suspicion or request discovered only one-fourth as many cases of syphilis as did the otherwise strictly comparable group of institutions in which a serologic test for syphilis was made as a routine. This can mean only that the former sanatoriums are missing 3 of 4 cases of syphilis. Wide differences of opinion in regard to antisyphilitic treatment in the presence of pulmonary tuberculosis were encountered, and there was no uniformity of practice in the different institutions. As the authors wryly point out, about the only discernible common factor was the tendency to give treatment once a week. In contrast to this, Guild and Nelson gained the impression that in a given institution, antisyphilitic treatment tended to be standardized and that if any treatment was given it was given in only one way, irrespective of the type of tuberculosis coexistent.

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143 Karnosh, L. J., and Connor, W. H. Syphilitic Pseudobulbar Palsy with Compulsive Weeping, *Am J Syph, Gonorr & Ven Dis* **20** 115 (March) 1936.

144 Winkelman, N. W. Syphilis of the Spinal Cord, *Am J Syph & Neurol* **19** 378 (July) 1935, *Am J Syph, Gonorr & Ven Dis* **20** 62 (Jan.), 421 (June) 1936.

145 Guild, C. St. C., and Nelson, M. The Problem of Coexisting Syphilis and Tuberculosis in Light of Current Opinion and Practice, *Am Rev Tuberc* **33** 31 (Jan.) 1936.

In a consideration of the interrelationships of tuberculosis, syphilis and antisyphilitic treatment Padget and Moore<sup>146</sup> point out that most of the studies of these interrelationships between the two diseases have been made from the point of view of those interested primarily in tuberculosis and that there is no uniformity of recorded opinion regarding the incidence of coexistence of the two diseases (i e, the tendency of one to predispose to the other), the effect of either one on the course of the other or the influence of antisyphilitic therapy on tuberculosis

Examination of the available information revealed that no study of the incidence of coexistence of the two diseases, including that from their own material, provides a basis for valid conclusions. In the opinion of these authors the question can never be solved by retrospective study but may be approached only by the preplanned observation of a large group of patients over a long period of time. The basic scheme for such a study is outlined

It is noted that there are numerous clinical impressions that active tuberculosis favorably modifies the course of syphilitic infection, but the authors emphasize the lack of definitive information in this regard and point out that this question may be solved, if at all, only by animal experimentation, the applications of which are limited in this field. Contrarily several carefully studied series of cases document the consensus of competent physicians that untreated syphilis adversely affects the course of tuberculous infection

The important point, however, is the effect on the patient of the introduction of antisyphilitic treatment into the picture of coexistent syphilis and tuberculosis. Reports from various hospitals for tuberculous patients indicate that mild antisyphilitic treatment reduces the mortality from tuberculosis and results in clinical improvement of the pulmonary infection of patients suffering from both diseases, as contrasted with appropriate control groups. This type of treatment, however, is totally inadequate for certain forms of syphilis (e g, dementia paralytica) which are more certainly fatal than even exudative pulmonary tuberculosis, and it is emphasized that the currently adopted attitude that tuberculosis is the more important disease when it coexists with syphilis is not necessarily correct

Finally, the authors report a series of 15 cases in all of which intensive antisyphilitic treatment had been closely followed by and probably had occasioned the fulminating development of previously unrecognized (and they believe unrecognizable) pulmonary tuberculosis

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146 Padget, P, and Moore, J E. The Interrelationships of Tuberculosis, Syphilis and Antisyphilitic Treatment, *Am Rev Tuberc* 33 10 (Jan) 1936

Collating this experience, they emphasize that the treatment of coexistent tuberculosis and syphilis must not be regarded as a routine matter in any instance in regard to either disease but must be determined by close cooperation between physicians expert in these fields

*Syphilis and Primary Glaucoma*—Beckh<sup>147</sup> investigated this subject and says

A study was made of the incidence of syphilis in a group of 355 consecutive public ward patients with primary glaucoma to establish if there is any basis, on clinical grounds, for the entity "primary syphilitic glaucoma," No relationship between syphilis and primary glaucoma was suggested by a comparative study, with various control groups, from the point of view of incidence, age of onset, and response to specific therapy A review of the manifestations of syphilis in patients with syphilis and primary glaucoma showed the luetic process to be latent in 82 per cent of the cases A study of 11 cases of buphthalmos did not point to an etiological connection with syphilis

*Late Effects of Adequate Antisyphilitic Therapy*—Hall<sup>148</sup> studied the mortality figures of insurance companies for patients who had had syphilis and sufficiently adequate treatment therefor to be granted life insurance subsequently and discovered an apparent tendency to prematurely early death in these patients from other diseases, notably tuberculosis and cancer He concludes

If further investigation and experience should prove the validity of the impressions and suppositions engendered by such a study as the present one, our forewarning will arm us with at least one potent weapon the recognition of the cured syphilitic's diminished resistance to certain diseases in particular If, by virtue of his past or present but latent disease, or by virtue of the extra load of antisyphilitic treatment he has borne, or both, he is recognized as probably being particularly susceptible to pulmonary tuberculosis, appendicitis, pneumonia and/or cancer, he can be given the advantage of all the appropriate knowledge which we have toward preventing and treating these conditions, when such susceptibilities are intelligently anticipated

#### CONGENITAL SYPHILIS

*The Diagnosis of Congenital Syphilis*—It has long been clear that the early institution of antisyphilitic therapy is as important in congenital as in acquired syphilis, but the former condition, on the average, presents a much more difficult problem for early diagnosis than the latter Under the conditions of modern practice a woman with syphilis rarely bears a child without the fact she has syphilis being discovered and at least some treatment administered This treatment, even though inadequate to protect the child from infection, almost always is enough to suppress the lesions, and the child is, at birth, apparently normal

147 Beckh, W Syphilis and Primary Glaucoma, Am J Ophth **18** 1129 (Dec) 1935

148 Hall, A F Undertreatment Versus Overtreatment of Syphilis, J Indiana M A **28** 586 (Nov) 1935

Serologic tests of blood from the cord are inadequate for early diagnosis, and the roentgenologically characteristic osseous lesions may not have developed, so valuable time may be lost before a diagnosis finally can be made. Impressed by this state of affairs, there have been a number of efforts to expedite the diagnosis. Ingraham<sup>149</sup> describes in detail the technic for dark field examination of material from the wall of the umbilical vein. If spirochetes are demonstrated the diagnosis of congenital syphilis is made within an hour of birth, but failure to find these organisms has no value in excluding infection of the child. Ingraham made a diagnosis of congenital syphilis by this method in more than a third of the instances in which the child later was proved by the more usual methods to be infected. Parmelee and Halpern,<sup>150</sup> in contrasting the efficiency of clinical, serologic and roentgenologic methods in the diagnosis of congenital syphilis, demonstrate the superiority of the latter, especially in children aged from 6 weeks to 3 months. Ingraham<sup>151</sup> verified the superiority of roentgenographic methods, and determined by the study of serial roentgenograms<sup>152</sup> that what he terms the "lag phase," i. e., the time which elapses between the infection with syphilis of the fetus and the appearance of roentgenologically demonstrable lesions, is five weeks for syphilitic osteochondritis and four months for syphilitic periostitis. He concludes, then, that a single roentgenogram taken when the infant is 6 weeks old should demonstrate the changes in practically every case, but that these may be found much sooner in many instances. He<sup>153</sup> finally sums up current opinion by contrasting the efficiency of the various diagnostic methods employed and emphasizes that a study of the ensemble is essential if the diagnosis is to be made at the earliest possible moment. Faber and Black<sup>154</sup> add a valuable observation. Under the term "Fildes' law" they restate Fildes' original observation thus: "Syphilitic reagin in the blood of the new-born infant is diagnostic not of syphilis in the infant but of syphilis in the mother." They observed, however, when they

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149 Ingraham, N. R. Congenital Syphilis. Diagnosis by Means of Dark-Field Examination of Scrapings from the Umbilical Vein, *J. A. M. A.* **105** 560 (Aug. 24) 1935.

150 Parmelee, A. H., and Halpern, L. J. The Diagnosis of Congenital Syphilis, *J. A. M. A.* **105** 563 (Aug. 24) 1935.

151 Ingraham, N. R. Roentgen-Positive Seronegative Infantile Congenital Syphilis, *Am. J. Dis. Child.* **50** 1444 (Dec.) 1935.

152 Ingraham, N. R. The Lag Phase in Early Congenital Osseous Syphilis. A Roentgenographic Study, *Am. J. M. Sc.* **191** 819 (June) 1936.

153 Ingraham, N. R. The Diagnosis of Infantile Congenital Syphilis During the Period of Doubt, *Am. J. Syph. & Neurol.* **19** 547 (Oct.) 1935.

154 Faber, H. K., and Black, W. C. Quantitative Wassermann Tests in Diagnosis of Congenital Syphilis. Clinical Importance of Fildes' Law, *Am. J. Dis. Child.* **51** 1257 (June) 1936.

quantitated the serologic test for syphilis on blood from the cord that usually the blood from infants who subsequently were shown to have syphilis was positive in high titer, whereas that from the ones subsequently proved to be normal was of low titer. Furthermore, the titer in the latter group was found to decrease in serial tests, as little as a week apart, which was not true of the former. They suggest, therefore, that serial quantitative serologic tests for syphilis in an infant under suspicion may save much time in establishing a diagnosis.

*Lesions of Congenital Syphilis*—Dorne and Zakon<sup>155</sup> call attention to the enlargement of the sternal end of one clavicle with consequent enlargement of the sternoclavicular articulation as a stigma of congenital syphilis. It was present in all of their group of 12 older children and adults with congenital syphilis. Doderlein<sup>156</sup> reports finding delay in the ossification of the petrous portion of the temporal bone in syphilitic fetuses, and Brown<sup>157</sup> found numerous intestinal lesions, which he describes as gummas but which were teeming with spirochetes (*S. pallida*), in a premature syphilitic infant who died an hour after birth. Reich<sup>158</sup> reports 5 cases of osteochondritis occurring in older (7 to 14 years) children with congenital syphilis. Since in the 4 who were treated for syphilis the osteochondritis promptly resolved, Reich considered it to be syphilitic in origin.

*The Treatment of Congenital Syphilis*—Smith<sup>159</sup> presents detailed analyses of the entire experience of the pediatric department of the Johns Hopkins Hospital.

Acetarsons in the Treatment of Congenital Syphilis. Traisman<sup>160</sup> has now extended his series of children with congenital syphilis treated

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155 Dorne, M., and Zakon, S. J. Enlargement of One Sternoclavicular Articulation as a Valuable Clinical Sign of Late Prenatal (Congenital) Syphilis, *Arch Dermat & Syph* **32** 602 (Oct) 1935.

156 Doderlein, W. Ueber den Einfluss der kongenitalen Lues auf die Verknocherung der Labyrinthkapsel beim Neugeborenen, *Arch f Ohren-, Nasen- u Kehlkopfh* **140** 229 (Jan 3) 1936.

157 Brown, A. F. Intestinal Lesions in Congenital Syphilis, *Arch Path* **21** 251 (Feb) 1936.

158 Reich, B. Osteochondritis syphilitica bei Lues congenita tarda. Spezifische Erkrankungen der Epiphysenlinien bei alteren Kindern mit kongenitaler Spätluës, *Beobachtungen an 5 Fällen*, *Deutsche Ztschr f Chir* **245** 437 (Sept) 1935.

159 Smith, F. R., Jr. Congenital Syphilis in Children. Results of Treatment in Five Hundred and Twenty-One Patients. I, *Am J Syph & Neurol* **19** 532 (Oct) 1935, II, *Am J Syph, Gonorr & Ven Dis* **20** 45 (Jan) 1936, Congenital Syphilis. The Results of Treatment in Children, *J A M A* **105** 409 (Aug 10) 1935.

160 Traisman, A. S. Further Observations on the Use of Acetarsons in the Treatment of Congenital Syphilis, *J Pediat* **7** 495 (Oct) 1935.

with acetarsone to 65, and his period of observation to three years. The early promise given by the original results from acetarsone therapy has in his opinion been fulfilled, and Traisman concludes that it is the ideal drug for the oral treatment of congenital syphilis in the infant. Davidson and Birt,<sup>161</sup> from experience with 37 children, are equally enthusiastic.

**Malaria Therapy** Wile and Hand<sup>162</sup> received replies to a questionnaire concerning 24 patients with juvenile dementia paralytica seen by them over a period of seven years. Half of the 10 who had not received treatment with malaria were dead, and the condition of the remainder was unchanged or worse. Two of 14 who received malaria therapy were improved, 2 were dead and the reports revealed the condition of the remainder to be unchanged or worse. Since those who received malaria treatment were in somewhat better condition when first seen than those in the other group, these authors believe that malaria is of little value in the treatment of juvenile dementia paralytica, and they conclude that to be effective malaria treatment of juvenile neurosyphilis must be given in the asymptomatic stage of the disease. Kidd,<sup>163</sup> who had used malaria in the treatment of a wide variety of forms of congenital syphilis with usually excellent results, is equally gloomy concerning the prognosis of clinically apparent juvenile neurosyphilis, with or without malaria therapy, but Palisa<sup>164</sup> reports complete or good remission in 10 (37 per cent) of 27 malaria-treated patients with juvenile dementia paralytica and slight remission in 5 others.

### THIRD GENERATION SYPHILIS

It has long been known and has been a matter of considerable interest that the transmission of syphilis from parent to child seldom goes beyond the second generation. There have been those, indeed, to contend that third generation syphilis does not occur. Stokes,<sup>165</sup> in his discussion of the subject, says in the first edition of his textbook, "Personally I have yet to see a report which is beyond cavil," but in

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161 Davidson, A. M., and Birt, A. R. The Treatment of Congenital Syphilis with Stovarsol, *Canad. M. A. J.* **34**: 33 (Jan.) 1936.

162 Wile, U. J., and Hand, E. A. Juvenile Dementia Paralytica, with Especial Reference to Its Treatment with Malaria, *J. A. M. A.* **105**: 566 (Aug. 24) 1935.

163 Kidd, R. A. Malaria Treatment in Congenital Syphilis, *Ohio State M. J.* **32**: 645 (July) 1936.

164 Palisa, C. Zur Therapie und Prognose der juvenilen Paralyse, *Wien klin. Wchnschr.* **48**: 716 (May 18) 1935.

165 Stokes, J. H. Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1926, p. 1054.

the second edition <sup>166</sup> he modifies this to read as follows "However, no reasonable doubt, albeit the extreme rarity is conceded, exists of third generation syphilis" In the latter edition, he cites the Fournier-Finger criteria, which in his opinion it is necessary to fulfil in order to establish a diagnosis of third generation syphilis 1 Acquired syphilis must be demonstrated in the grandmother 2 The syphilis of the mother must be proved to be congenital, and the father must be healthy 3 The third generation child must have indisputable congenital syphilis 4 Manifestations must have appeared in both the second and the third generation soon after birth

In this light there have been several interesting reports Rosenbaum <sup>167</sup> observed 2 families and describes 4 children of the third generation with congenital syphilis with a background almost fulfilling the Fournier-Finger criteria, and the cases of Boardman <sup>168</sup> and Valentova <sup>169</sup> seem conclusive Elliott <sup>170</sup> adds to the Fournier-Finger criteria the previously taken for granted requirement that the parentage of the child suspected of third generation syphilis must be certain He adds another case report, which is not entirely conclusive

#### SYPHILIS AND PREGNANCY

Cole <sup>171</sup> reports the results of the study of the 603 women in the material studied by the Cooperative Clinical Group who had, under observation, 922 pregnancies after their syphilitic infection, the final outcome of which was known for 607 The important conclusions are 1 Congenital syphilis is essentially a preventable disease 2 Its prevention depends on "the routine, early and repeated use" of a serologic test for syphilis in every pregnant woman 3 Once the diagnosis of syphilis is made its prevention depends on intensive antisyphilitic treatment of the mother 4 The pregnant woman tolerates antisyphilitic treatment well 5 Therapy begun before the fifth month of pregnancy is more certain to protect the fetus than treatment begun later, but even a little treatment late in pregnancy greatly improves the chance that the child will be nonsyphilitic 6 To insure that her child

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166 Stokes, J H Modern Clinical Syphilology, ed 2, Philadelphia, W B Saunders Company, 1934, p 1271

167 Rosenbaum, H A Third Generation Syphilis, J Pediat **7** 797 (Dec) 1935

168 Boardman, W P Syphilis in the Third Generation, Arch Dermat & Syph **32** 660 (Oct) 1935

169 Valentova, O Syphilis in 3 Generationen, abstr, Zentralbl f Haut- u Geschlechtskr **53** 205 (April 5) 1936

170 Elliott, A Third-Generation Syphilis, Brit M J **1** 1206 (June 13) 1936

171 Cole, H, and others Cooperative Clinical Studies in the Treatment of Syphilis Syphilis in Pregnancy, J A M A **106** 464 (Feb 8) 1936



will be normal, every woman known to have had syphilis should be given antisyphilitic treatment throughout every pregnancy, irrespective of the clinical status or the results of serologic tests

Exner,<sup>172</sup> employing the questionnaire method which is generally utilized by the American Social Hygiene Association for gathering information, attempted to determine current clinic and private patient practice directed toward the prophylaxis of congenital syphilis. For clinic practice he concludes that while progress in this regard is evident, there is still great need for earlier diagnosis and early adequate treatment and there is an urgent demand for a better follow-up of children born of mothers with syphilis, in order not only to determine the outcome for the child but also to allow evaluation of the results of antepartum antisyphilitic therapy. Private practitioners, however, still evince considerable reluctance toward employing serologic tests for syphilis as a routine in their practice, although half of those who replied to the questionnaire reported that they did so.

*Syphilis of the Placenta*—It has already been emphasized that the early diagnosis of congenital syphilis depends on an evaluation of the ensemble, in which no small place has been given<sup>153</sup> to the histologic appearance of the placenta. The report from Montgomery,<sup>173</sup> therefore, is disturbing to the orthodox. This author, in a restudy of sections from a large number of placentas, concludes that while unquestionably the placenta can transmit *S. pallida* from mother to fetus, the organ itself is singularly resistant to syphilitic infection. The areas of placental fibrosis, which others have considered diagnostic of syphilis of the placenta, this author says are not a pathologic entity, and when present in great numbers in the placenta from a syphilitic premature stillbirth, are a phenomenon of the prematurity and not of syphilis.

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172 Exner, M. J. Syphilis in Pregnancy. Report of a Study, J. A. M. A. **106** 488 (Feb. 8) 1936.

173 Montgomery, T. L. Fibrosis of the Placenta. Its Significance in the Normal and in the Syphilitic Organ, Am. J. Obst. & Gynec. **31** 253 (Feb.) 1936.

## Book Reviews

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**Medical Mycology Fungous Diseases of Men and Other Mammals** By Carroll William Dodge Price, \$10 Pp 900, with 142 illustrations St. Louis C V Mosby Company, 1935

This comprehensive volume is the result of ten years of study and of collecting material in the field of mycology The book has chapters dealing with the general morphology of fungi and their physiology, culture mediums, methods of isolation, microscopy and nomenclature Then follow sixteen chapters dealing with specific groups of fungi according to the author's classification

It must be granted at the outset that few, if indeed any, working in those fields of medicine in which mycologic lesions are likely to be encountered have even a working knowledge of this greatly jumbled-up subject The thousands of species described and the various and numerous classifications proposed have made the subject a nightmare to all serious students The author, although he has done a monumental piece of work, unfortunately has not clarified the field, and by giving an entirely new classification with many new names has left the reader in an unending labyrinth It is also unfortunate that the title suggests the inclusion of material which is not to be found in the pages of the monograph, and the physician will have his curiosity by no means satisfied, there being practically no treatment of the medical side of mycology In addition, numerous species of fungi which have no significance in medicine, as for example the dozens of species of *Actinomyces*, are discussed, yet strangely enough one finds neither in the index nor under the description of species any mention of *Actinomyces hominis* If the author intended to include it under *Actinomyces bovis*, no indication of the fact is given

The author has slipped many times into a curious and clearly incorrect error in nomenclature When in placing a species in a different genus he has found the specific name preoccupied, he has correctly given the species a new name but has added "Dodge, n sp" to the name Clearly this is not correct, since the species still belongs to the original author Examples of this error are unfortunately found in the name of the organism causing torula infection in man and also the one causing Madura foot

Undoubtedly the greatest contribution the author has made in this book is listing the hundreds, perhaps thousands, of references to the literature up to the end of the year 1933 These have all the earmarks of having been carefully compiled, yet the reviewer has found that the references are not readily available, first, because there is no author index and, second, because the references are collected at the end of each chapter Since the author has used an entirely new classification, one is often in a quandary as to where to look for specific references, further, references are not keyed into the text

All in all this volume represents a huge amount of work in an important and chaotic field While the author has not produced a solution to the general problem and has certainly not filled the great need for a practical medical mycology, he has, so to speak, in the words of one who is not a mycologist, put us "on our way"

**Undersøgelser over nogle metalsaltes indvirkning paa fagocytose** By Paul Mørch Paper Pp 224, with 7 illustrations and 47 tables Copenhagen: Nyt Nordisk Forlag, 1933

The experimental work described in this dissertation was done at the University of Copenhagen and is fundamental, its immediate importance concerning chiefly

immunology and general physiology The body of the text is in Danish, but a detailed summary in readable German is given on pages 210 to 219 and should be called to the attention of any one who wishes to attempt work in this difficult field, since some of the sources of error in the determinations of phagocytic activity are only beginning to be appreciated The influence of the salts of thirty-nine metals on phagocytosis was studied Thirty-three were found to possess optimum concentrations at which they stimulated phagocytosis These optima lay distributed within wide limits ( $10^{-1}$  to  $10^{-10}$  molar), and no relation was found between the position of the metallic element in the periodic table and its optimum concentration for phagocytosis The stimulation in the case of calcium, zinc, manganese and nickel amounted (at the optimum) to from 200 to 250 per cent more than that in the controls Antimony, arsenic, erbium, lead, palladium and selenium were never found to stimulate phagocytosis, and the maximum obtained for mercuric salts was only 100 per cent above that of the controls

**Lobar Pneumonia and Serum Therapy** By Frederick T Lord, M D, and Roderick Heffron, M D Price, \$1 Pp 91, with 11 illustrations London Oxford University Press, 1936

Some five years ago the Commonwealth Fund financed a study of pneumonia in Massachusetts This booklet summarizes in a clinical way the results of this work

The volume is an engaging monograph, clearly written, well printed and illustrated with simple diagrams One unfamiliar with technic learns how to type pneumonia sputum by the Newfeld method, how to test a patient for sensitivity to serum and how best to administer antipneumococcus serum in properly selected cases One learns of the expected results of the modern treatment of pneumonia In Massachusetts during the last five years, patients with pneumonia, infected with type I or type II Pneumococcus, whose condition was recognized early and who received serum as quickly as possible fared well, on the whole

A book of this character, so convenient for physicians and medical students to read and so full of common ungarnished sense is almost certain to be universally popular The Commonwealth Fund and the authors are to be congratulated for presenting the results of their complicated study of public health in such a simple and useful manner

**Immunology** By Noble P Sherwood, M D, Professor of Bacteriology, University of Kansas Price, \$6 Pp 608, with 8 colored plates and 27 other illustrations St Louis C V Mosby Company, 1935

Sherwood states that this book was written for medical students and for other persons who have had training in pathogenic bacteriology or inorganic and organic chemistry and who are interested in the underlying principles involved in infection, resistance and diagnostic laboratory tests It is a nicely arranged, clearly written book, giving plain descriptions of various technical procedures, and is well printed and well illustrated It has three features which will have great appeal to students At the end of each chapter is a carefully chosen bibliography referring to the topic under discussion and stimulating wider reading Near the end of the book is an authors' index which, among other information, gives one a fair idea of the present leaders in the field of immunology And, finally, there is an excellent subject index, so that any information, from the definition of ablastin to facts about zootoxins, is easily obtainable On the whole, the book belongs to that attractive species which at once feels at home and is a useful member of the family in any library, on any reference shelf or in any laboratory

## CALCIUM AND IODINE METABOLISM IN THYROID DISEASE

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AND

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A disturbance of the calcium balance has been found in thyroid disease<sup>1</sup> Apparently there is a relationship between the calcium and iodine intake, the normal function of the thyroid gland and the development of goiter<sup>2</sup> Consequently, we became interested in determining any existing correlation between the total calcium and iodine metabolism and thyroid disease in man

For at least a century calcium has been considered a factor in the production of goiter As early as 1837 McClelland<sup>3</sup> reported this belief The iodine deficiency theory of goiter, which has been accepted by

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This investigation has been aided by a grant from Mr William Wallace Kincaid, Ellerslie-on-Niagara, New York

From the Department of Medical and Surgical Research, the University Hospital, and the Department of Surgery of the Ohio State University

1 Aub, J C , Bauer, W , Heath, C, and Ropes, M Studies of Calcium and Phosphorus Metabolism III The Effects of the Thyroid Hormone and Thyroid Disease, *J Clin Investigation* **7** 97, 1929

2 (a) Tanabe, H Experimenteller Beitrag zur Aetiologie des Kropfes, *Beitr z path Anat u z allg Path* **73** 415, 1925 (b) Hellwig, C A Iodine Deficiency and Goiter Influence of a Diet Poor in Iodine on the Thyroid Gland in White Rats, *Arch Path* **11** 709 (May) 1931, Experimental Goiter Functional, Chemical and Histologic Studies, *ibid* **19** 364 (March) 1935 (c) Thompson, J Influence of the Intake of Calcium on the Thyroid Gland of the Albino Rat, *ibid* **16** 211 (Aug) 1933, The Influence of Calcium and Iodine on Growing Rats, *Endocrinology* **17** 537, 1933 (d) Klem, J The Effect of Calcium on the Storage of Colloid in the Thyroid Gland, *Ann Int Med* **7** 1080, 1934, The Correlation of Mineral Metabolism and the Vegetative Nervous System in Thyroid Disease, *ibid* **8** 798, 1935

3 McClelland, J W On the Connection Between Goiter and Cretinism Their Nature and Causes, Some Inquiries in the Province of Kemaon Relative to Geology and Other Branches of Natural Science, Including an Inquiry into the Causes of Goiter, Calcutta, 1835, Dublin *J M Sc* **11** 295, 1837

many, was advocated by Maffoni<sup>4</sup> in 1846, by Prevost<sup>5</sup> in 1849 and by Chatin<sup>6</sup> in 1852

Reviews of the earlier literature on calcium metabolism in thyroid disease have been presented<sup>7</sup> However, until Aub and his associates<sup>1</sup> reported their systematic studies in 1929, the evidence for a disturbance of calcium metabolism remained inconclusive The true nature of this disturbance remains unknown Hansman and Wilson<sup>8</sup> did not accept Aub's<sup>1</sup> thesis that thyroxine has a direct catabolic effect on the calcium deposits in bone Aub and his associates<sup>9</sup> stated that they did not consider the increased excretion of calcium as assisting in the excretion of acid metabolites, nor did they find it influenced by the administration of viosterol<sup>10</sup>

The literature on iodine feeding, on the absorption of iodine and on the food, blood, thyroid and urinary iodine in health and in thyroid disease, with substantiatory and supplemental data, has already been presented by Curtis and his associates<sup>11</sup> The studies of the total iodine

4 Maffoni, A C Brevi cenni sullo stato sanitario del piemonte con proposta di alcuni mezzi per giungere a migliorarlo, *Atti d Accad di med di Torino* **2** 453, 1846

5 Prevost, J L, quoted by Orr and Leitch<sup>18</sup>

6 Chatin, A Recherche de l'iode dans l'air, les eaux, le sol et les produits alimentaires des alpes de la France et du Piedmont, *Compt rend Acad d sc* **33** 529, 1851, **34** 14 and 51, 1852

7 Golden, R, and Abbott, H The Relation of the Thyroid, the Adrenals and the Islands of Langerhans to Malacic Diseases of Bone, *Am J Roentgenol* **30** 641, 1933 Aub and others<sup>1</sup>

8 Hansman, F S, and Wilson, F H Calcium and Phosphorus Metabolism in Diseases of the Thyroparathyroid Apparatus I Calcium, Phosphorus and Total Metabolism in Hyperthyroidism and the Part Played by the Parathyroid Glands, *M J Australia* **1** 37, 1934

9 Albright, F, Bauer, W, and Aub, J C Studies of Calcium and Phosphorus Metabolism VIII The Influence of the Thyroid Gland and the Parathyroid Hormone upon the Total Acid-Base Metabolism, *J Clin Investigation* **10** 187, 1931

10 Tibbetts, D M, McLean, R, and Aub, J C Studies of Calcium and Phosphorus Metabolism XX The High Calcium Excretion in Exophthalmic Goiter Is Not Due to Vitamine D Deficiency, *J Clin Investigation* **11** 1273, 1932

11 (a) Phillips, F J, Erf, O, and Curtis, G M The Effects of Prolonged Increased Iodine Feeding, *Ohio J Sc* **35** 286, 1935 (b) Cole, V V, Dunn, R H, and Curtis, G M The Intrapulmonic Absorption of Iodine, *J Pharmacol & Exper Therap* **53** 327, 1935 (c) Cole, V V, Curtis, G M, and Bone, M L The Iodine Content of Hospital Foods, *J Am Dietet A* **10** 200, 1934 (d) Davis, C B, Curtis, G M, and Cole, V V Blood Iodine Studies II The Normal Iodine Content of Human Blood, *J Lab & Clin Med* **19** 818, 1934 (e) Curtis,

metabolism of normal subjects and of patients with thyroid disease reported to date have been few<sup>12</sup> This literature was reviewed recently<sup>13</sup> At present the chief reason for the inability of investigators to interpret the interrelationship of calcium and iodine metabolism to the function of the thyroid gland is a lack of firmly established facts concerning the total metabolism of either calcium or iodine

Recently, the experimental evidence of Zondek and Reiter,<sup>14</sup> Tanabe,<sup>2a</sup> Abelin,<sup>15</sup> Hellwig,<sup>2b</sup> Thompson,<sup>2c</sup> Klein<sup>2d</sup> and of others has been considered indicative of an interrelationship between calcium and iodine in the production of goiter However, Remington and Levine<sup>16</sup> stated that varying the calcium content and the calcium-phosphorus ratio of the goitrogenic diet does not significantly affect the degree of goiter produced in the rat

This report is concerned with the presentation of the results of an investigation of the calcium and iodine balance made pretherapeutically of one patient with hypothyroidism, two normal subjects and two patients with exophthalmic goiter

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G M , Cole, V V , and Phillips, F J The Blood Iodine in Thyroid Disease, *West J Surg* **42** 435, 1934 (f) Curtis, G M Iodine Metabolism in Toxic Goiter, *J Med* **15** 294, 1934 (g) Curtis, G M , and Phillips, F J The Urinary Excretion of Iodine I The Loss of Iodine in the Urine Following Thyroidectomy, *J Clin Investigation* **13** 777, 1934 (h) Curtis, G M , Davis, C B , and Phillips, F J Significance of the Iodine Content of Human Blood, *J A M A* **101** 901 (Sept 16) 1933 (i) Curtis, G M , Barron, L E , and Phillips, F J Blood Iodine Studies V Blood Iodine After Total Thyroidectomy in Man, *J Lab & Clin Med* **20** 813, 1935 (j) Matthews, N L , Cole, V V , and Curtis, G M The Urinary Excretion of Iodine II The Normal Urinary Iodine in Central Ohio, to be published (k) Cole, V V , and Curtis, G M Cyclic Variations in Urinary Excretion of Iodine in Women, *Proc Soc Exper Biol & Med* **31** 29, 1933

12 (a) von Fellenberg, T Untersuchungen über den Jodstoffwechsel I Versuche mit physiologischen Jodmengen beim Erwachsenen, *Biochem Ztschr* **142** 246, 1923, (b) Das Vorkommen, der Kreislauf und der Stoffwechsel des Jods, *Ergebn d Physiol* **25** 176, 1926 (c) Scheffer, L Ueber die Jodbilanz normaler Menschen, *Biochem Ztschr* **11** 259, 1933, Jodstoffwechsel bei Schilddrüsenerkrankten, *Klin Wchnschr* **12** 1285, 1933, Jodstoffwechsel bei Hyperthyreosen, *ibid* **13** 1570, 1934

13 Cole, V V , and Curtis, G M Human Iodine Balance, *J Nutrition* **10** 493, 1935

14 Zondek, H , and Reiter, I , quoted by Marine, D The Pathogenesis and Prevention of Simple and Endemic Goiter, *J A M A* **104** 2334 (June 29) 1935

15 Abelin, I Schilddrüse und Mineralstoffwechsel Einfluss des Dinatriumphosphats und der Calciumsalze auf die Wirkung der Schilddrüsen-substanzen, *Biochem Ztschr* **199** 72, 1928

16 Remington, R E , and Levine, H Personal communication to the authors

## EXPERIMENTAL METHODS

The principles underlying the choice of diet in the investigation of mineral metabolism have been discussed by many<sup>17</sup> The constant diet which we used, selected and begun by each subject two or three days prior to this investigation, was of a low calcium and sufficient iodine content, adequate in other respects and as attractive as possible One patient with exophthalmic goiter was maintained on a high calcium intake All foods known to be rich in iodine were excluded<sup>11c</sup> The normal iodine requirements for man are not definitely known The minimum daily requirement for a man has been stated as 45 micrograms<sup>18</sup> Eggenberger<sup>19</sup> stated that from 40 to 80 micrograms probably covers the daily need for iodine Our usual hospital diet has been considered of sufficient iodine content<sup>11c</sup> The diets of patients G L and E K were probably at the lower limits of sufficiency The caloric value was calculated as basal plus 20 to 30 per cent The daily intake of protein was 1 Gm per kilogram The intake of salt and fluid as well as the acid-base values of the diet were maintained within a narrow range This diet had a low fat content The five subjects remained at rest in bed under special care throughout the period of study They did not lose weight Only one research worker and one assistant were permitted to give the patients food and water and to take care of the urine and feces The loss of iodine through perspiration and expiration was minimized by the rest in bed and by careful adjustment of the temperature of the room

This investigation was divided into periods of three days each Equal weights of food were taken for consumption and for analysis The food of each period for analysis was dried in an evaporating dish, ground, thoroughly mixed and weighed Urine was collected in twenty-four hour specimens, preserved in an icebox, measured and diluted to 2,000 cc Analyses were made on the mixed three day specimen The feces for each period were marked off by carmine in the usual manner These were dried, ground in a grinding mill, well mixed, weighed and preserved for analysis

## LABORATORY METHODS

Various methods have been described for the determination of the calcium content of urine, food and feces These methods have the disadvantage of requiring

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17 Bauer, W , Albright, F, and Aub, J C Studies of Calcium and Phosphorus Metabolism II The Calcium Excretion of Normal Individuals on a Low Calcium Diet, *J Clin Investigation* 7 75, 1929 Lusk, G The Science of Nutrition, ed 4, Philadelphia, W B Saunders Company, 1928 Barker, L F , Hoskins, R G , and Mosenthal, H O Endocrinology and Metabolism, ed 1, New York, D Appleton & Co , 1922 Stewart, C P , and Percival, G H Calcium Metabolism, *Physiol Rev* 8 283, 1928 Sherman, H C The Chemistry of Food and Nutrition, ed 4, New York, The Macmillan Company, 1933 Hansman and Wilson<sup>8</sup>

18 Orr, J B , and Leitch, I Iodine in Nutrition, Medical Research Council, Special Report Series, no 123, London, His Majesty's Stationery Office, 1929

19 Eggenberger, H , cited by Marine, D The Pathogenesis and Prevention of Simple or Endemic Goiter, *J A M A* 104 2334 (June 29) 1935

expensive apparatus and of being laborious and time consuming<sup>20</sup> or of incompletely oxidizing the organic matter<sup>21</sup> In this laboratory we have devised a perchloric acid method for the determination of the calcium content Perchloric acid, when concentrated and hot, is a more powerful oxidizing agent than sodium persulfate, which is used in the Shohl-Pedley method,<sup>21a</sup> or of sulfuric acid, which is often used for wet ashing<sup>22</sup> Bumping and spattering are much less likely to occur than when sulfuric acid is used The oxidation is smoother and more rapid and complete The whole procedure is carried out in one specially made centrifuge tube<sup>23</sup> Qualitative and not quantitative transfer and filtration are avoided

A sample, containing the amount of calcium suitable for the Clark-Collip<sup>24</sup> method of determining the calcium content of the blood, is first oxidized with perchloric acid Precipitation, washing of the precipitate and titration with potassium permanganate are then carried out according to the principles set forth by McCrudden,<sup>20a</sup> Shohl,<sup>25</sup> Shohl and Pedley<sup>21a</sup> and Clark and Collip<sup>24</sup> The method as applied to urine is as follows

1 To 5 or 10 cc of urine in a 75 cc specially made pyrex centrifuge tube add 2 cc of perchloric acid (60 per cent) per five cubic centimeters of urine

2 Gently evaporate the contents of the tube for a few minutes over a microburner or an ordinary burner until the heavy white fumes of perchloric acid arise One or two drops of caprylic alcohol may be used to prevent foaming

3 When the contents of the tube turn brown, add concentrated nitric acid, drop by drop, until the solution becomes clear and colorless or slightly yellow

4 When all the organic matter has been oxidized, allow the contents of the tube to cool somewhat and then dissolve the perchlorates with 30 cc of water

5 Add 10 cc of normal oxalic acid

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20 (a) McCrudden, F H The Determination of Calcium in the Presence of Magnesium and Phosphates The Determination of Calcium in Urine, *J Biol Chem* **10** 187, 1911-1912 (b) Van Slyke, D D, and Sendroy, J, Jr Gasometric Determination of Oxalic Acid and Calcium, and Its Application to Serum Analysis, *ibid* **84** 217, 1929

21 (a) Shohl, A T, and Pedley, F G A Rapid and Accurate Method for Calcium in Urine, *J Biol Chem* **50** 537, 1922 (b) Stearns, G A Rapid Method for the Preparation of Fecal Digests Suitable for Use in Nitrogen and Mineral Analyses, *J Lab & Clin Med* **14** 954, 1929

22 Neumann, A Eine Veraschungsmethode (Sauregemisch-Veraschung) und vereinfachte Bestimmungen von Eisen, Phosphorsäure, Salzsäure und anderen Aschenbestandteilen unter Benutzung dieser Sauregemisch-Veraschung, *Ztschr f physiol Chem* **37** 115, 1902 Stearns<sup>21b</sup>

23 The pyrex centrifuge tube is conical, with a capacity of 75 cc, and sufficiently narrow at the bottom (2 or 3 mm, inner diameter) to hold together the precipitate and permit none to escape when the fluid is decanted It has a tip of thick glass This tube may be purchased from the Kauffman-Lattimer Co, Columbus, Ohio

24 Clark, E P, and Collip, J B A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, *J Biol Chem* **63** 461, 1925

25 Shohl, A T The Effect of Hydrogen Ion Concentration upon the Determination of Calcium, *J Biol Chem* **50** 527, 1922



6 Adjust the  $p_H$  ( $p_H$  4 to 5.6) of the solution with concentrated ammonium hydroxide so as just to exceed the end-point, and complete the adjustment with 10 per cent hydrochloric acid until a pink color is obtained, using 1 drop of methyl red (0.2 in 50 per cent alcohol) as the indicator

7 Let stand overnight Centrifugate for ten minutes at 1,500 revolutions per minute and wash three times with ammonium hydroxide (0.5 per cent) by the Clark-Collip method<sup>24</sup> of decantation

8 Redissolve the calcium oxalate precipitate in 10 cc of normal sulfuric acid Heat to 70 or 80 C

9 Titrate with hundredth normal potassium permanganate and calculate

This method, with slight modifications, was applied also to food and feces

In order to test the accuracy of this method several experiments (table 1) were carried out No effort was made to obtain the highest degree of accuracy,

TABLE 1—*Data on the Accuracy of the Method Employed*

Theoretical Solutions					Recovery of Added Calcium				
Calcium Taken,* Mg	Uric Acid Added, Mg	Perchloric Acid (60%), Cc	Calcium Found, Mg	Deviation, Mg	Urine,† Cc	Calcium Added, Mg	Calcium Obtained, Mg	Added Calcium Recovered, Mg	Deviation, Mg
0.00	0	4	0.00		10	0.00	0.53		
0.00	10	4	0.00		10	0.00	Lost		
0.88	0	4	0.90	+0.02	10	0.00	0.54		
0.88	0	4	0.89	+0.01	10	0.88	1.44	0.90	+0.02
0.88	10	4	0.89	+0.01	10	0.88	1.46	0.92	+0.04
0.88	10	4	0.90	+0.02	10	0.88	1.45	0.91	+0.03

\* The theoretical solution of calcium used in this experiment was made by dissolving 0.22 Gm of calcium carbonate (calcite for standardizing, obtained from the General Chemical Co., code no 1791, obtained through the Kauffman Lattimer Co., Columbus, Ohio) in 10 cc of calcium free concentrated hydrochloric acid plus double distilled water and diluted to 1 liter with double distilled water The uric acid (10 per cent) was calcium free

† The samples were obtained from the same specimen of urine

the results represent those obtainable by an analyst of moderate experience These results (table 1) compare favorably with those obtained by the usual wet ashing method

The calcium content of the blood was determined by the Clark and Collip<sup>24</sup> method The phosphorus content was determined by the King<sup>26</sup> method The iodine content of the blood, urine, water, food, sweat and feces of normal subjects was determined<sup>13</sup> by the Phillips and Curtis<sup>27</sup> method and that of patients with thyroid disease<sup>28</sup> by the McCullagh<sup>29</sup> method

All analyses were made in duplicate and were repeated when adequate checks were not obtained

26 King, E J The Colorimetric Determination of Phosphorus, *Biochem J* **26** 292, 1932

27 Phillips, F J, and Curtis, G M Blood Iodine Studies IV The Clinical Determination of Iodine in Blood, Urine and Feces, *Am J Clin Path* **4** 346, 1934

28 Dr Versa V Cole gave permission for us to use these data.

29 McCullagh, D R A New Method for the Determination of Iodine, *J Biol Chem* **107** 35, 1934

Two normal subjects were studied. The calcium values were comparable to those obtained by other investigators,<sup>30</sup> whose data have been reviewed<sup>17</sup>

#### NORMAL CONTROLS

E S, a white taxicab driver, single, aged 27, volunteered for this experiment. He had always enjoyed good health. Clinical examination showed no abnormalities. He had previously received no iodine or iodized salt.

Laboratory examination revealed negative Wassermann and Kahn reactions of the blood. Moderate anemia was present. The leukocyte and differential counts were normal. The urine was normal. The basal metabolic rate on Dec 3, 1933, was minus 1, with the basal pulse rate 59, the temperature 97.6 F, the respiratory rate 12, the blood pressure 100 systolic and 70 diastolic and the weight 121 pounds (55 Kg.)

*Comment*—The calcium and phosphorus contents of the blood (table 2) averaged 10.5 and 4.1 mg, respectively, which are normal. The fecal excretion of calcium was greater than the urinary excretion. This subject, with a low calcium intake of 696 mg per three day period, showed a continuous but normal negative calcium balance. The total excretion of calcium was 153 per cent of the intake.

The blood iodine averaged 13.4 micrograms per hundred cubic centimeters, which is normal. The urinary excretion of iodine was greater than the fecal excretion. This subject, with a sufficient iodine intake, 468 micrograms per three day period, was in continuous positive iodine balance. The urinary and fecal excretion of iodine was about 50 per cent of the intake of iodine.<sup>13</sup> These data are presented in table 2.

G L, a white woman of 31, a worker in a shoe factory, volunteered as a normal subject for this investigation. Her general health was good at the time of this study. Clinical examination showed no abnormalities. She had received no iodine or iodized salt previous to hospitalization. Laboratory examination revealed that the blood and urine were normal. The Wassermann and Kahn reactions of the blood were negative. The Graham-Cole test for hepatic function gave negative results. The basal metabolic rate on Feb 4, 1934, was minus 10, with the basal pulse rate 69, the temperature 98.2 F, the respiratory rate 15, the blood pressure 110 systolic and 70 diastolic and the weight 108 pounds (49 Kg.)

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30 Sherman, H. C. Calcium Requirements of Maintenance in Man, *J Biol Chem* **44**:21, 1920. Rose, M. S. Experiments on the Utilization of the Calcium of Carrots by Man, *ibid* **41**:349, 1920. Bogert, L. J., and Kirkpatrick, E. E. Studies in Inorganic Metabolism. II The Effects of Acid Forming and Base Forming Diets upon Calcium Metabolism, *ibid* **54**:375, 1922. Sherman, H. C., Wheeler, L., and Yates, A. B. Experiments on the Nutritive Value of Maize Protein and on the Phosphorus and Calcium Requirements of Healthy Women, *ibid* **34**:383, 1918. Sherman, H. C., Gillett, L. H., and Pope, H. M. Monthly Metabolism of Nitrogen, Phosphorus and Calcium in Healthy Women, *ibid* **34**:373, 1918. Sherman, H. C., Winters, J. C., and Phillips, V. Efficiency of Oat Protein in Adult Human Nutrition, *ibid* **34**:53, 1919.

TABLE 2—Data for E S, a Normal White Man \*

Date When Period Started	Weight, Kg	Calcium				Iodine			Blood			Basal Meta bolic Rate, %					
		Output		Intake, Gm	Balance, Gm	Output		Intake, Balance, Megm Megm	Date	Serum Cal- cium, Mg per 100 Cc	Serum Phos- phorus, Mg per 100 Cc		Iodine, Megm per 100 Cc				
		Urine, Gm	Feces, Gm			Total, Gm	Urine, Megm †							Feces, Megm	Total, Megm		
1	12/ 6/33	55 0	0 104	1 206	1 310	0 657	-0 653	154	114	263	469	+201	12/ 3/33 12/ 6/33	10 4	4 2	11 9	- 1 - 6
2	12/ 9/33	53 5	0 404	0 524	0 928	0 713	-0 215	137	58	195	505	+310	12/ 7/33 12/10/33	10 6	4 4	15 7	-15
3	12/12/33	53 0	0 572	0 664	1 236	0 670	-0 566	161	89	250	469	+219	12/12/33	10 5	3 7	12 6	
4	12/15/33		0 315	0 460	0 775	0 725	-0 050	130	93	223	449	+226	12/13/33	10 5	3 7	12 6	
5	12/18/33		0 272	0 805	1 077	0 718	-0 359	142	48	190	451	+261	12/20/33	10 5	3 7	12 6	
Average for entire period		53 8	0 333	0 732	1 065	0 696	-0 369	145	80	225	468	+243	Average	10 5	4 1	13 4	- 7

\* E S was 23 years old. He received a diet containing 1,900 calories, with 55 Gm of protein.

† A microgram equals 0.001 mg. It is frequently called a gamma.

*Comment*—The calcium and the phosphorus content of the blood (table 3) averaged 101 and 46 mg per hundred cubic centimeters, respectively, which are normal values. The fecal excretion of calcium was greater than the urinary excretion. This subject, with a low calcium intake, 984 mg per three day period, showed a normal negative calcium balance. The total excretion of calcium was 102 per cent of the intake.

The blood iodine averaged 79 micrograms per hundred cubic centimeters, which is a low normal value. The urinary excretion of iodine was greater than the fecal excretion.<sup>13</sup> This subject, with an intake of 168 micrograms of iodine per three day period, showed a continuous positive iodine balance. The urinary and fecal excretion of iodine was 80 per cent of the intake of iodine. These data are presented in table 3.

#### HYPOTHYROIDISM

E. K., a white housewife aged 38, was mildly myxedematous. She was readmitted to the University Hospital for this investigation after total thyroidectomy for essential hypertension four and a half months previously.

Data concerning the total thyroidectomy are presented elsewhere.<sup>31</sup> In the interval her general health had been good. The blood pressure had returned to its original level of about 210 systolic and 130 diastolic, nevertheless, some symptomatic improvement had been noted. The headaches in the occipital region had largely disappeared. There was evidence of an early stage of myxedema. The patient complained of lethargy and said she always felt cold. There had been a gain in weight. She said she had taken no thyroid medication or iodized salt after the total thyroidectomy.

Physical examination revealed essentially no abnormality, except for the elevated blood pressure. No dependent edema was noted. No objective signs of hypoparathyroidism were disclosed. The blood showed a slight anemia, with a decreased hemoglobin content. On February 13 examination of the blood showed 5,050 leukocytes, with 56 per cent neutrophils, 6 per cent eosinophils, 2 per cent basophils, 18 per cent lymphocytes and 18 per cent monocytes. Urinalysis revealed no abnormality, except for a trace of albumin. The Wassermann and Kahn tests of the blood were negative. After the intravenous injection of phenolsulfonphthalein there was elimination of 40 per cent of the dye at the end of one hour, and of 5 per cent at the end of the second hour. The nonprotein nitrogen content of the blood was 33 mg per hundred cubic centimeters. An electrocardiogram showed evidence of first degree heart block and suggested myocardial damage. The basal metabolic rate on February 12 was minus 25, with the basal pulse rate 63, the temperature 98 F, the respiratory rate 12, the blood pressure 190 systolic and 130 diastolic and the weight 131 pounds (60 Kg).

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31 Curtis, G. M., Barron, L. E., and Matthews, N. L. The Urinary Excretion of Iodine. II. The Loss of Iodine in the Urine Following Total Thyroidectomy in Man, to be published.

TABLE 3—*G L, a Normal White Woman*\*

Period	Date When Started	Weight, Kg	Calcium				Iodine				Blood			Basal Meta- bolic Rate, %			
			Output		Intake, Gm	Balance, Gm	Output		Intake, Balance, Mmegm Mmegm	Date	Serum Cal- cium, Mg per 100 Cc	Serum Phos- phorus, Mg per 100 Cc	Iodine, Mmegm per 100 Cc				
			Urine, Gm	Feces, Gm			Total, Gm	Urine, Mmegm							Feces, Mmegm	Total, Mmegm	
1	2/ 7/34	50	0 408	0 608	1 010	1 075	+0 059	107	25	132	168	+36	2/ 4/34				-10
2	2/10/34		0 366	0 557	0 923	0 884	-0 039	107	19	126	171	+45	2/ 8/34	9 1	4 3	9 0	
3	2/13/34		0 378	0 546	0 924	0 862	+0 038	109	29	138	163	+25					
4	2/16/34		0 402	0 490	0 892	0 994	+0 102	94	29	123	164	+41	2/19/34	10 9	4 8	7 2	
5	2/19/34	50	0 408	0 857	1 265	1 004	-0 261	101	33	134	173	+39	2/23/34			7 5	
Average for entire period			0 392	0 612	1 004	0 984	-0 020	104	27	131	168	+37	Average	10 0	4 6	7 9	-10

\* G L was a normal white woman aged 31. She received a diet containing 1,500 calories, with 50 Gm of protein.

*Comment*—The calcium content of the blood (table 4) averaged 89 mg per hundred cubic centimeters, which is normal. The urinary excretion of calcium was greater than the fecal excretion. This patient, with a low calcium intake, 377 mg per three day period, was in continuous negative calcium balance. This balance was less than that of normal subjects with such a low calcium intake. The total excretion of calcium was 153 per cent of the intake.

The value for blood iodine averaged 5.4 micrograms per hundred cubic centimeters, which is below normal. The urinary excretion of iodine was greater than the fecal excretion.<sup>13</sup> This subject, with an iodine intake of 117 micrograms per three day period, was in continuous positive iodine balance. The urinary and fecal excretion of iodine was approximately 80 per cent of the intake of iodine. The value for sweat iodine also was determined for this patient.<sup>13</sup> These data are shown in table 4.

#### EXOPHTHALMIC GOITER

T. F., a white housewife aged 24, was transferred on April 9, 1934, to the Research Surgical Service for this investigation and for thyroidectomy.

Since November 1932 she had been aware of nervousness, tachycardia, dyspnea, tremor of the upper extremities and emotional and heat instability. She had noted exophthalmos for about one year. She had noted the presence of a goiter for a month. She had received no iodine for at least two months previous to this investigation. Physical examination showed no evidence of disease other than that referable to exophthalmic goiter.

Laboratory investigation revealed the blood and urine to be normal. The Wassermann and Kahn tests of the blood were negative. A roentgenogram of the hands showed no detectable evidence of decalcification. Plummer and Dunlap<sup>32</sup> have presented the reports of patients who showed roentgenologic osteoporosis due to decalcification. The basal metabolic rate on April 2 was plus 61 per cent, with the basal pulse rate 103, the temperature 99 F, the respiratory rate 30, the blood pressure 148 systolic and 84 diastolic and the weight 124 pounds (56 Kg).

Under hospital management alone this patient showed a remission of the clinical manifestations. There was a fall in the basal metabolic rate over a period of twenty-three days to plus 25 per cent on April 25, with the basal pulse rate 103, the temperature 97.2 F, the respiratory rate 19, the blood pressure 128 systolic and 70 diastolic and the weight 127 pounds (58 Kg). The investigation was terminated on April 27. Five cubic centimeters of diiodotyrosine (10 mg of iodine) was then given daily at noon beginning on April 30. This had little further effect on the basal metabolic rate. On May 5 the basal metabolic rate was plus 21 per cent, with the basal pulse rate 98, the temperature 98 F, the respiratory rate 15 and the weight 134 pounds (61 Kg). Thyroidectomy was accomplished on May 10. Eighty grams of characteristic diffuse hyperplastic goiter was removed. Microscopic examination showed extensive and generalized iodine-induced colloid involution. There was a definite differential involution with a minimal amount of vacuolation. The colloid was thin and granular. There was considerable hyperinvolution. Round cell infiltration was minimal.

32 Plummer, W. A., and Dunlap, H. F. Cases Showing Osteoporosis Due to Decalcification in Exophthalmic Goiter, *Proc. Staff Meet., Mayo Clin.* 3: 119, 1928.

TABLE 4—Data for E K, a Woman with Myxedema\*

Period	Date When Started	Weight, kg	Calcium				Iodine				Blood			Basal Meta bolic Rate, %			
			Output		Intake, Gm	Balance, Gm	Urine, Megm	Output		Intake, Balance, Megm	Serum Cal cium, Mg per 100 Cc	Serum Phos phorus, Mg per 100 Cc	Iodine, Megm per 100 Cc				
			Urine, Gm	Feces, Gm				Total, Gm	Fees, Megm						Total, Megm		
1	4/11/34	60.5	0.345	0.215	0.560	0.414	-0.146	72	27	99	123	+24	11/22/33 2/12/34	9.0 8.4	4.4	6.1 6.0 4.2	-22 -28
2	4/11/34	60.5	0.324	0.272	0.596	0.340	-0.256	60	30	90	111	+21	4/15/34 4/17/34 4/18/34	9.2	4.3	—	—
Average for entire period		60.5	0.335	0.243	0.578	0.377	-0.201	66	29	95	117	+23	Average	8.9	4.4	5.4	-25

\* E K was a 38 year old housewife. Myxedema had followed total thyroidectomy (Nov 21, 1933) for essential hypertension. She received a diet containing 1,240 calories, with 50 Gm of protein.

*Comment*—The calcium and the phosphorus content (table 5) averaged 10.3 and 3.9 mg per hundred cubic centimeters of blood, respectively, which is normal. The fecal excretion of calcium was greater than the urinary excretion. Even with the high calcium intake of 2,455 mg per three day period, this patient was in *continuous, moderately increased negative balance*. The total excretion of calcium was 144 per cent of the intake of calcium.

The value for blood iodine averaged 26 micrograms per hundred cubic centimeters, which is considerably above normal. The fecal excretion of iodine was greater than the urinary excretion<sup>13</sup>. This patient, with an intake of 466 micrograms of iodine per three day period, was, exclusive of the sweat iodine, in low positive iodine balance. The urinary and fecal excretion of iodine was about 96 per cent of the intake of iodine. The differences in the excretion of iodine by E. S., a normal control, and this patient with hyperthyroidism are largely accounted for by the greater excretion of iodine in the feces of the latter. The value for sweat iodine was determined also for this patient<sup>13</sup>. These data are given in table 5.

R. S., a white housewife aged 24, entered the University Hospital for this investigation and for thyroidectomy on Oct. 30, 1934. She had had nervousness, tachycardia, palpitation, emotional and heat instability, polyphagia, polydipsia and polyuria since April, at which time she first noted exophthalmos. Six weeks before her admission to the hospital she became aware of a goiter. Since that time the size of the goiter had fluctuated considerably, the gland being more prominent during menstruation. The patient had taken a proprietary preparation containing iodine for from two to four weeks previous to this investigation. The physical examination, except for the observations referable to the exophthalmic goiter, revealed no essential abnormality.

Laboratory examination revealed that the blood and urine were normal. The hemoglobin value was slightly decreased. The Wassermann and Kahn tests of the blood were negative. The Scott-Reinhart test for pregnancy was negative. Roentgenograms of the hands showed no detectable evidence of decalcification. The basal metabolic rate on November 5 was plus 81 per cent, with the basal pulse rate 112, the temperature 98.6 F, the respiratory rate 24, the blood pressure 130 systolic and 50 diastolic and the weight 103 pounds (47 Kg).

With hospital management the patient showed a slight remission of the clinical manifestations. Over a period of seventeen days the basal metabolic rate decreased only slightly (to plus 68 per cent) on November 22, with the basal pulse rate 107, the temperature 98.8 F, the respiratory rate 11, the blood pressure 142 systolic and 68 diastolic and the weight 100 pounds (45 Kg). The investigation was completed on November 17, and iodine medication (10 mg daily, given as potassium iodide) was begun immediately. This medication had a marked effect on the basal metabolic rate. On November 25 the basal metabolic rate was plus 38 per cent, with the basal pulse rate 95, the temperature 97.8 F, the respiratory rate 11 and the weight 102 pounds (46 Kg). Thyroidectomy was accomplished on November 28. Sixty-two grams of characteristic diffuse hyperplastic goiter was removed. Microscopic examination showed a variable iodine-induced colloid involution, some evidence of early nodule formation and extensive lymphocytic infiltration with localized aggregations.



TABLE 5—Data for T F, a Woman with Exophthalmic Gout<sup>\*</sup>

Date When Period Started	Weight, Kg	Calcium				Iodine				Blood			Basal Meta- bolic Rate, %				
		Output		Intake, Gm	Balance, Gm	Output		Urine, Megm	Feces, Total, Megm	Intake, Balance, Megm	Date	Serum Cal- cium, Mg per 100 Cc		Serum Phos- phorus, Mg per 100 Cc	Iodine, Megm per 100 Cc		
		Urine, Gm	Feces, Gm			Total, Gm	Urine, Megm									Feces, Total, Megm	
1	4/12/34	57.5	0.651	3.156	3.807	1.996	-1.811	138	282	420	502	+82					
2	4/15/34		0.363	2.999	3.362	2.762	-0.600	189	271	460	465	+5	4/16/34			+23	
3	4/18/34		0.474	3.812	4.286	2.748	-1.538	132	293	425	493	+68					
4	4/21/34		0.444	2.454	2.898	2.422	-0.476	189	284	473	424	-49	4/23/34 4/25/34		26	+25	
5	4/24/34	57.5	0.348	3.058	3.406	2.348	-1.058	138	272	410	446	+36	5/ 4/34		3.5		
Average for entire period		57.5	0.456	3.096	3.552	2.455	-1.097	157	280	437	466	+29	Average		10.3	3.9	+26

<sup>\*</sup> T F was 24 years old. She received a diet containing 3,350 calories, with 57 Gm of protein.

*Comment*—The calcium and the phosphorus content (table 6) averaged 104 and 48 mg per hundred cubic centimeters of blood, respectively, which is normal. The fecal excretion of calcium was greater than the urinary excretion. This patient, with a low calcium intake, 942 mg per three day period, was in continuous and greatly increased negative calcium balance. The total excretion of calcium was 314 per cent of the intake.

The value for blood iodine was 22 micrograms per hundred cubic centimeters, which is moderately above normal. The fecal excretion of iodine was greater than the urinary excretion<sup>13</sup>. This patient, with a sufficient iodine intake, 653 micrograms per three day period, was in continuous negative iodine balance. The urinary and fecal excretion of iodine was 117 per cent of the intake of iodine. The value for sweat iodine was determined also for this patient<sup>13</sup>. Table 6 presents these data.

#### COMMENT

The calcium and the phosphorus content of the blood of all five subjects varied within normal limits. The patient with hypothyroidism showed a higher than normal retention of calcium. In the two normal subjects with a low calcium diet the calcium balance was negative. The two patients with exophthalmic goiter showed an increase in the excretion of calcium. In one the increase was almost entirely by way of the feces. In the other the increase was by way of both the urine and the feces, and this resulted in a continuous negative calcium balance greater than normal. These data are readily appreciated by an inspection of the accompanying chart. They confirm the investigations of Aub and his co-workers<sup>1</sup> on the total calcium metabolism as related to thyroid disease in man and those of Pugsley and Anderson<sup>33</sup> for the rat. Hypotheses as to the cause of this increase in the amount of calcium excreted have been advanced<sup>34</sup>. It is possible that the loss of calcium is due to a combination of factors, the underlying cause of which is the increased utilization of thyroid hormone by the tissues.

The value for blood iodine of the normal subjects averaged 107 micrograms per hundred cubic centimeters<sup>13</sup>. For the patient with hypothyroidism the value for blood iodine averaged 54 micrograms per hundred cubic centimeters, which is low. The value for blood iodine of the two patients with exophthalmic goiter averaged 24 micrograms per hundred cubic centimeters, which is high. Normal subjects and those with hypothyroidism were in continuous positive iodine balance. The

<sup>33</sup> Pugsley, L. I., and Anderson, E. The Effect of Desiccated Thyroid, Irradiated Ergosterol and Ammonium Chloride on the Excretion of Calcium in Rats, *Biochem J* 28 754, 1934.

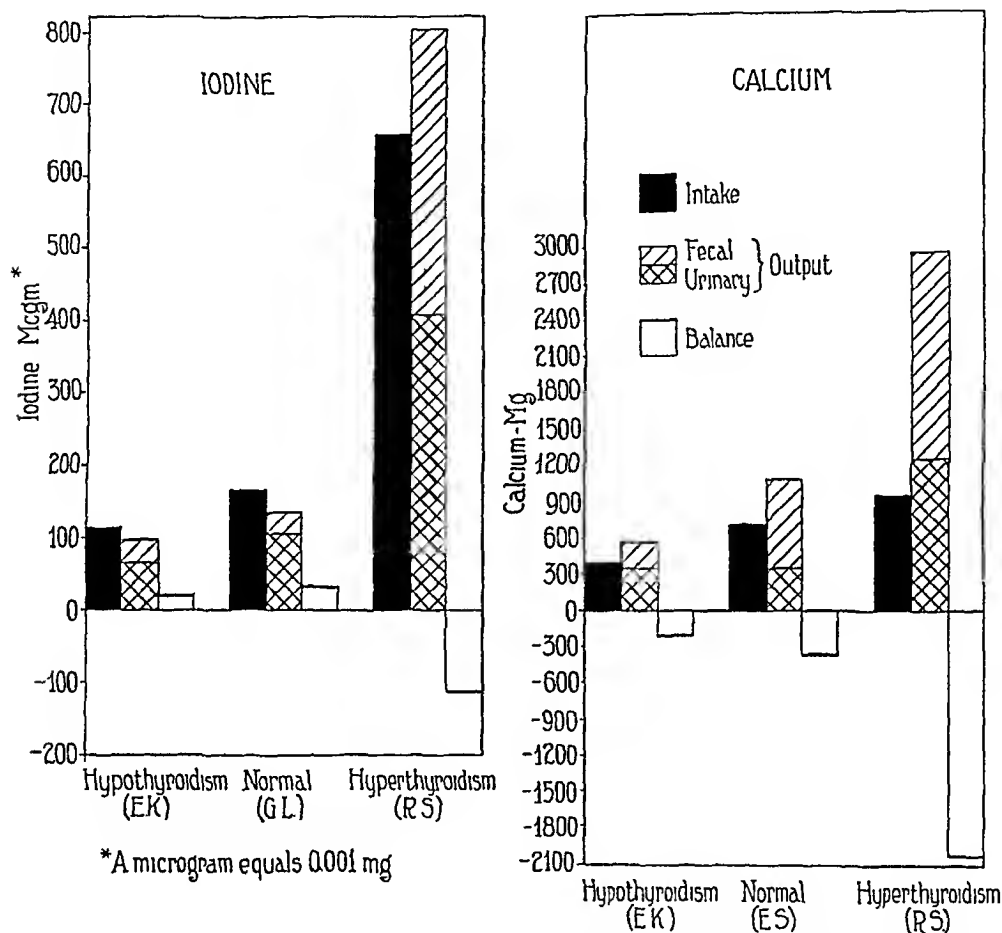
<sup>34</sup> Aub, Bauer, Heath and Ropes<sup>1</sup> Hansman and Wilson<sup>8</sup> Albright, Bauer and Aub<sup>9</sup> Tibbetts, McLean and Aub<sup>10</sup>

TABLE 6—Data for R S, a Woman with Exophthalmic Goiter \*

Period	Date When Started	Weight, Kg	Calcium					Iodine				Blood			Basal Meta bolic Rate, %	
			Output			Intake, Gm	Balance Gm	Output		Intake, Balance, Megm	Date	Serum Cal eum, Mg per 100 Cc	Serum Phos phorus, Mg per 100 Cc	Iodine, Megm per 100 Cc		
			Urine, Gm	Feces, Gm	Total, Gm			Urine, Megm	Feces, Megm							Total, Megm
1	11/ 8/34	47 0	1 188	1 641	2 829	0 883	-1 946	204	398	597	495	-102	11/ 6/34			+81
2	11/11/34	48 0	1 059	1 742	2 801	0 943	-1 858	345	135	480	462	- 18	11/ 9/34 11/19/34			+84 +65
3	11/14/34	46 5	1 506	1 752	3 258	1 000	-2 258	516	699	1,215	1,002	-213	11/22/34 11/24/34 11/25/34	10 4	4 8	+68
Average for entire period		47 0	1 251	1 712	2 963	0 942	-2 021	355	409	764	653	-111	Average	10 4	4 8	+75

\* R S was 24 years old She received a diet containing 3,800 calories, with 50 Gm of protein

urinary loss of iodine was greater than the fecal excretion. In one patient with exophthalmic goiter the iodine balance was continuously negative. In the other patient also it was less than that of the two normal controls. In both the increased fecal excretion of iodine was greater than the increased urinary excretion of iodine, thus showing a difference from normal subjects and those with hypothyroidism. These results are presented in the accompanying chart. They are in agreement with the findings of Fellenberg<sup>12a, b</sup> for normal subjects, of



A comparison of the average calcium and iodine values for a patient with hypothyroidism (E K) and a patient with hyperthyroidism (R S) with those for normal controls (G L and E S)

Scheffer<sup>35</sup> for normal subjects and for patients with exophthalmic goiter and of Schittenhelm and Eisler<sup>36</sup> for an adult with myxedema

These results show that the thyroid gland is a principal organ in maintaining the iodine content of the blood at an average normal level

35 Scheffer, L. Ueber die Rolle des Jods bei der Entstehung von Schilddrüsenerkrankheiten, Schweiz med Wchnschr 64 969, 1934 Scheffer<sup>12c</sup>

36 Schittenhelm, A, and Eisler, B. Der Jodstoffwechsel des Myxodematosen, Ztschr f d ges exper Med 80 589, 1932

From investigations made subsequent to total thyroidectomy on E K and on others<sup>37</sup> it is obvious that the true picture of iodine metabolism cannot be determined by a study of the blood iodine alone. Such study determines principally the amount of mobile iodine. It does not indicate the destiny of the iodine, and it reveals nothing of its origin, storage, utilization or excretion.

Fellenberg<sup>12b</sup> pointed out that the storage of iodine is of two types: first, a temporary, readily available storage, which he located in the thyroid gland, and, second, a more permanent, less easily mobilizable storage, which, he theorized, may be located in the thyroid gland, the blood or possibly in the liver or elsewhere. His researches, however, had not extended this far. The results noted in the case of E K and also in other cases<sup>37</sup> suggest that the extrathyroid tissues contain a readily available supply of iodine, as indicated by the immediate and great rise in the urinary excretion of iodine subsequent to total thyroidectomy. They suggest also that the more permanent storage of iodine is extrathyroid, since the characteristic slow mobilization and elimination of the element continue even after the total removal of the thyroid gland. It may be that this iodine is located in the cellular protein.

Abelin<sup>38</sup> produced a thyroxine-like substance by artificially iodizing protein. This had a calorogenic effect on totally thyroidectomized rats. He concluded that there is an extrathyroid substance in the organism which has a similar physiologic action, a substance which he called homothyroxine. It is possible that this is one of the factors which maintains the basal metabolism in a totally thyroidectomized patient and prevents it from decreasing more than 30 or 40 per cent. It is well known that the thyroid gland is not necessary for vegetative or invertebrate life, and these researches suggest that the gland is not absolutely necessary for the biologic utilization of iodine, its hormone merely increasing the availability of iodine for utilization by the tissues. Further researches on the latter phases of iodine metabolism should prove of the greatest importance.

The true cause of the increase in the fecal excretion of iodine in exophthalmic goiter is not known. It may be due to an increased concentration of iodine as the inorganic iodide of calcium or as an addition product of calcium iodide. Greenbaum and Raiziss<sup>39</sup> showed that the elimination of iodine after the administration of calcium iodide orally and of an addition product of calcium iodide and thio-urea orally or

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37 Curtis, Barron and Phillips<sup>11i</sup> Curtis, Barron and Matthews<sup>31</sup>

38 Abelin, I. Ueber die extrathyreoidale Entstehung thyroxinartig wirkender Jodverbindungen, *Klin Wchnschr* **13** 940, 1934

39 Greenbaum, E R, and Raiziss, G W. The Elimination of Iodine After Oral or Intravenous Administration of Various Iodine Compounds in Single Massive Doses, *J Pharmacol & Exper Therap* **30** 407, 1927

intravenously is entirely different from that subsequent to the administration of sodium or potassium iodide or some organic iodine compounds. Approximately one-half appears in the urine and the remainder in the feces. The iodides of potassium and sodium were eliminated almost quantitatively in the urine. Calcium iodide and its addition products were eliminated more slowly than these other compounds. Furthermore, in partial support of this hypothesis is the occurrence of an increased content of inorganic iodine in the blood in exophthalmic goiter<sup>40</sup> and an increase in the fecal excretion of calcium.

These results emphasize also that the body may excrete an element of which it is in apparent need. This is not applicable to chlorine or to the more permanent storage of iodine which is husbanded by the body. During starvation the excretion of chlorine and of iodine which is mobilized with difficulty<sup>12b</sup> sinks almost to zero. The true significance of this increased negative iodine balance in exophthalmic goiter in the presence of an intake of iodine sufficient for normal subjects and in the presence of an apparent need for iodine remains unknown. This chemical manifestation of the disease becomes still more significant when it is realized that the diffuse hyperplastic thyroid gland retains its natural avidity for iodine, such as in compound solution of iodine or even in diiodotyrosine.

The true fate of thyroid hormone in the organism is, as yet, unknown. But, suffice it to say that in exophthalmic goiter not only the hormonal fraction of the blood but also the other organic fractions and the inorganic fraction of iodine are increased<sup>40</sup>. Elmer and Luczynski<sup>41</sup> have shown also that after gastric administration or intravenous injection of thyroxine into animals, from 90 to 93 per cent of the iodine excreted in the bile and from 49 to 63 per cent of the iodine excreted in the urine are excreted as split products of thyroxine. In addition, Asimoff and Estrin<sup>42</sup> recently found that after feeding dried thyroid gland to dogs and after the intravenous injection of thyroxine the amount of iodine excreted in the urine was increased. This urine in no

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40 Elmer, A. W., Rychlik, W., and Scheps, M. L'hyperthyroxinémie dans la thyrotoxicose, *Compt rend Soc de biol* **117** 533, 1934.

41 Elmer, A. W., and Luczynski, Z. Sur l'élimination par la bile de la thyroxine administrée par voie entérale, *Compt rend Soc de biol* **115** 647, 1933, Sur la décomposition par le foie de la thyroxine injectée dans les veines, *ibid* **114** 351, 1933.

42 Asimoff, G., and Estrin, E. Ueber das Schicksal des Schilddrüsenhormons im Organismus hyperthyreoidisierter Tiere, der Charakter des Ausscheidungs des Schilddrüsenhormons nach peroraler Einführung getrockneter Schilddrüse beim Hunde, *Ztschr f d ges exper Med* **76** 380, 1931, Ueber das Schicksal des Schilddrüsenhormons im Organismus hyperthyreoidisierter Tiere, der Charakter der Ausscheidung des Schilddrüsenhormons nach Einführung von Thyroxin per os, *ibid* **76** 399, 1931.

instance affected metamorphosis of the axolotl. They concluded that the iodine is excreted in the urine in simple compound form.

Elmer<sup>43</sup> has already shown, by giving a moderate dose of diiodotyrosine to men, that one half of the amount given is excreted in the urine in inorganic form. It is possible that some of this iodine is utilized thyroid hormone iodine in such chemical combination that it is not available to the thyroid gland for the formation of its hormone or to the tissues for their utilization. Further investigation of these particular problems concerning the ultimate fate of the thyroid hormone is needed.

In the patient with hypothyroidism a decrease in the amount of calcium excreted accompanied the decrease in the amount of circulating iodine. In the two patients with exophthalmic goiter an increase in the amount of calcium excreted was associated with the increase in the amount of circulating iodine.

In the patient with exophthalmic goiter who was maintained on a low calcium intake, a study of three periods of three days each revealed the iodine balance to be continuously negative and the calcium balance to vary directly with the iodine balance. In the patient with exophthalmic goiter maintained on a high intake of calcium, a study of five periods of three days each showed that the iodine balance remained at a level definitely lower than that in the two normal controls. The calcium balance varied inversely with the iodine balance. In the other subjects maintained on a low calcium diet, a study of nine of twelve periods of three days each showed that the calcium balance varied directly with the iodine balance.

An interpretation from these data of the correlation of the total calcium and iodine metabolism with the function of the thyroid gland should be made with caution, since only these five subjects, to our knowledge, have been so investigated thus far.

#### SUMMARY

An investigation of the calcium and iodine metabolism of one totally thyroidectomized patient, two normal subjects and two patients with exophthalmic goiter is reported.

An accurate, more simple and rapid method of determining the calcium content of the urine is presented.

The calcium and phosphorus content of the serum of one totally thyroidectomized subject and two patients with exophthalmic goiter was not appreciably changed.

In the patient with hypothyroidism there was an increased retention of calcium over normal. In the two normal subjects on a low calcium

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<sup>43</sup> Elmer, A. W. Di-Iodotyrosine and Thyroid Function, *Quart J Exper. Physiol* **24** 95, 1934.

diet the calcium balance was negative. In the two patients with exophthalmic goiter there was an increase in the amount of calcium excreted. In one the increase was almost entirely in the feces. In the other the increase was in both the urine and the feces. This resulted in a continuous negative calcium balance greater than normal.

The thyroid gland is the chief organ which maintains the blood iodine at an average normal level.

A study of the blood or of the urinary calcium or iodine alone does not reveal a complete picture of the calcium or iodine metabolism.

The extrathyroid tissues, as well as the thyroid gland, contain a readily available storage of iodine. The more permanent storage of iodine is extrathyroid.

In the two patients with exophthalmic goiter the iodine balance was less than normal even in the presence of an intake of iodine which was at least normally adequate. The increased fecal excretion of iodine was greater than the increased urinary excretion of iodine, thus showing a difference from the findings for normal persons and for subjects with hypothyroidism.

In the patient with hypothyroidism a decrease in the excretion of calcium accompanied the decrease in the circulating iodine. In the two patients with exophthalmic goiter an increase in the excretion of calcium accompanied the increase in the circulating iodine.

In the patient with exophthalmic goiter maintained on a low intake of calcium, observations during three periods of three days each revealed that the iodine balance was continuously negative and that the calcium balance varied directly with the iodine balance.

In the patient with exophthalmic goiter maintained on a high intake of calcium, observations during five periods of three days each showed that the iodine balance remained at a level definitely lower than that of the two normal controls. The calcium balance varied inversely with the iodine balance.

In the other subjects maintained on a low calcium diet, observations during nine of twelve periods of three days each showed the calcium balance to vary directly with the iodine balance.



# A SPECIFIC INFECTION CHARACTERIZED BY MULTIPLE ULCERS OF THE SMALL INTESTINE

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The purpose of this paper is to present an unusual and, as far as I know, unique infectious disease, which was characterized especially by a peculiar type of ulceration of the small intestine, from which a specific bacillus was isolated. This organism was capable of reproducing the disease and causing similar lesions in the monkey (*Macacus rhesus*)

In addition to enteritis there were other specific lesions, such as cholecystitis, cholangitis, pneumonitis, necrosis of the bone marrow and interstitial nephritis, all of which were reproduced in the monkey after the intravenous injection of the gram-negative bacillus isolated from the patient's bile and intestine

The clinical features of the case also were anomalous and presented many problems of diagnostic interest, as the following abstract will show

*History*—Mrs E B, a 54 year old inhabitant of a small town in the middle of the state of Tennessee, was admitted to the Vanderbilt Hospital on Feb 13, 1935, in a semicomatose condition. The history obtained was admittedly inadequate owing to the patient's condition. Three months previously she had consulted her local physician because of pain in the region of the liver and slight jaundice. Five weeks before admission to the hospital she was treated for an insect bite on the dorsum of one foot. This responded well to local treatment. About a week later she had a shaking chill and complained of generalized aching. After that she remained ill, with a morning and evening rise in temperature (to from 101 to 103 F). The urine was said to have contained pus. There was diarrhea, but no description of the stools could be obtained. She had taken little food or fluid for several days before her admission to the hospital.

*Physical Examination*—The significant findings were as follows. The temperature was 101.6 F, the pulse rate 104 and the respiratory rate 28. The patient was apathetic and had a yellowish pallor. She was lying perfectly still in bed. She looked ill, and her answers were delayed, short and difficult to understand. Ophthalmoscopic examination revealed a small hemorrhage just inferior to the right disk and a diffusely white area suggestive of old exudate above this disk. The vessels were slightly tortuous. The conjunctivae and mucous mem-

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Aided by a grant from the Division of Medical Sciences of the Rockefeller Foundation.

branes were pale. Fine crackling râles were heard at the base of each lung, and there were several areas of tubular breathing. The apex of the heart was in the left anterior axillary line. There was an occasional extrasystole, but no murmurs were present. The blood pressure was 94 systolic and 46 diastolic. The liver was felt 1 fingerbreadth below the right costal margin. There was tenderness in the right upper quadrant of the abdomen, but no masses were felt. All the normal reflexes were equally active but weak. No Babinski or Kernig reflex was present. On rectal examination large external hemorrhoids were noted, one of them containing a fresh clot. No rectal masses were felt. On removal the examining finger was streaked with brownish blood.

*Laboratory Observations*—A catheter specimen of urine showed albumin (2+), an acid reaction, a specific gravity of 1.012, from 5 to 10 white blood cells per high power field, no erythrocytes and only an occasional granular cast.

On February 14 the blood count showed 5,000 leukocytes, 20 per cent polymorphonuclears, 63 per cent lymphocytes, 16 per cent monocytes, 1 per cent myelocytes, 1,430,000 erythrocytes and 5.5 Gm of hemoglobin. The color index was 1.3. There was no striking variation in the size or shape of the erythrocytes, and their staining properties varied only slightly. A few normoblasts were present. No parasites were noted. The Wassermann and Kahn tests of the blood were negative. On February 14 the nonprotein nitrogen content of the blood was 86 mg per hundred cubic centimeters, and on February 18 it was 133 mg. The blood sugar content was 121 mg per hundred cubic centimeters.

The patient's serum failed to show significant agglutinations against *Bacillus typhosus*, *Bacillus paratyphosus* A and B, *Bacillus melitensis*, *Bacillus abortus* and *Bacillus tularensis*. On February 14 culture of the blood was sterile.

The cerebrospinal fluid was clear and contained no globulin. There were 4 cells.

Examination of the stool on February 16 showed that it was dark green and formed. It contained bile and occult blood but no parasites.

Roentgenograms showed right dorsal scoliosis. The left ventricle of the heart was slightly enlarged. There was a definite increase in the bronchovascular markings throughout the left lung and the upper lobe of the right lung. Calcified glands were present in the apex of the right lung. No exudation or consolidation was present.

Gastric analysis showed that free hydrochloric acid was absent. The total acid was 57 degrees during fasting. After the administration of alcohol free acid was still absent, and the total acidity was 25 degrees. No histamine was given because of the patient's condition.

*Course*—Because of the severe anemia the patient was given two transfusions of 500 cc of blood (on February 15 and 16) with slight, if any, benefit. The temperature remained high, from 102 to 104 F. On the evening of February 16 Cheyne-Stokes respiration developed, and the patient became comatose. The following day from 400 to 500 cc of bright red liquid blood was passed by rectum, it did not come from the external hemorrhoids. The respiration became shallow and rapid. The blood pressure was 100 systolic and 40 diastolic. The next morning (February 18) the blood pressure fell to 70 systolic and 20 diastolic, and the pulse rate increased. The patient failed to respond to caffeine and hypodermoclysis and expired from an undetermined cause on the fifth day of hospitalization.

*Gross Postmortem Observations*—There were ecchymotic spots on each arm, particularly at the elbow. A few smaller subcutaneous hemorrhages were seen

over other parts of the body. The conjunctivae were pale, and there were two petechiae in the right eye. There was a punched-out ulcer in the mucous membrane of the mouth at the junction of the upper lip and the upper jaw. The upper edge of a plate replacing the upper teeth just reached and was in contact with this ulcer.

**Serous Cavities** All the serous cavities were normal, except the pleural cavities, which had a few old adhesions.

**Heart** The heart weighed 300 Gm and showed no abnormality.

**Lungs** About half the upper lobe of the right lung was red and congested, it fairly dripped fluid. This area was firmer than the remainder of the lung, and crepitation was diminished, suggesting an early stage of a pneumonic process with edema.

**Gastro-Intestinal Tract** The mucosa of the stomach appeared atrophic and had many petechial hemorrhages. No ulcers were present either in the stomach or in the duodenum. Beginning at a point in the jejunum about 3 feet (92 cm) distal to the duodenojejunal flexure there were occasional places where the mucosal folds were slightly thicker, firmer and more prominent than normal. Some of these areas of thickening measured no more than 4 or 5 mm in diameter. In several there was a sharp umbilication in the center, at the base of which was hemorrhage. The ulcers became more numerous and larger in the lower portion of the jejunum. At the junction of the jejunum and the ileum there were ulcers at intervals of not more than 12 inches (30 cm) characterized by round, raised edges and a dirty grayish center. Blood was present in some of the craters. These ulcers appeared to be confined to the mucosa and submucosa. They occupied various positions in relation to the circumference of the intestine, however, most of them were near the mesenteric attachment. The serosa opposite the ulcers had no tubercle formation or other abnormality. In general the ulcers increased in size as the ileocecal valve was approached, where the largest one measured about 3 cm in diameter. The ulcers showed no definite relation to the lymphoid tissue. Most of Peyer's patches were inconspicuous, and certainly they were not hyperplastic. In one instance an ulcer encroached partly on a Peyer patch without any apparent involvement of the remainder of the patch. The terminal 30 inches (76 cm) of the ileum had several of these ulcers per foot (30 cm). There was one firm nodule in the first portion of the ileum, which measured about 5 mm in diameter, it was raised about 3 mm above the surrounding mucosa and had an ulcerated but not umbilicated surface. Smears and cultures were made from material taken from this and also from the umbilicated ulcers.

No ulcers were found in the cecum or colon. In the descending colon and sigmoid flexure there were about twenty small diverticula. These measured only a few millimeters in diameter and contained blood that varied from bright red to a dark hue. There was an internal hemorrhoid.

The contents of the duodenum and jejunum were covered with bile. The terminal portion of the ileum and the colon contained dark red, blood-tinged fecal material. The mesenteric nodes were not enlarged, and they appeared normal.

**Liver** The liver weighed 1,910 Gm. Minute yellow dots suggested necrosis. The gallbladder was distended with golden brown, cloudy bile. A culture was taken with aseptic technic before the organ was opened. There were no stones, and the mucosa was not remarkable grossly.

**Spleen** The spleen weighed 290 Gm. On the cut surface a uniformly red pulp everted the capsule. The organ was fairly firm and somewhat friable. The malpighian bodies were not prominent. The spleen was highly cellular, with the



Fig 1—*A*, the terminal portion of the ileum, showing ulcers which have no fixed relation to the lymphoid tissue or to the circumference of the intestine *B*, cross-section of the lower portion of the jejunum, showing ulceration in an inflammatory nodule,  $\times 16$



Fig 2—*A*, photomicrograph of a vessel in an inflammatory nodule of the intestine, showing inflammation, an early stage of necrosis and beginning thrombosis,  $\times 600$  *B*, two lymphatic vessels in an inflammatory nodule of the intestine loaded with large mononuclear cells,  $\times 500$  *C*, cross-section of the liver, showing inflammation about the portal area, cholangitis and periportal necrosis,  $\times 100$  *D*, cross-section of the gallbladder, showing inflammation of the wall, particularly about a vessel in the submucosa which is loaded with mononuclear phagocytes and leukocytes. There is a small area of necrosis just below the vessel,  $\times 100$



Fig 3—*A*, section of the lung, showing an area of inflammation and necrosis with an early stage of abscess formation. Such lesions are not in association with the bronchi but of vascular origin,  $\times 100$ . *B*, section of the kidney, showing focal accumulations of lymphocytes, mononuclear phagocytes and plasma cells in the interstitial tissue,  $\times 100$ .



appearance and increased size of an acute splenic tumor of the red type. However, it was firmer than is usually the case in typhoid.

**Pancreas and Adrenal Glands** These organs were normal.

**Kidneys** The right kidney weighed 240 Gm and the left 215 Gm. The capsule stripped off with ease, leaving a smooth, pale, swollen surface with a few petechial hemorrhages. The cortical striations were not distinct and regular, but there was no narrowing of the cortex. There were opaque focal areas in the cortex which were thought to represent necrosis. Considerable peripelvic hemorrhage was noted in each kidney, and there were petechial hemorrhages in the mucosa of the pelves and ureters. The right pelvis and ureter were slightly dilated, but no contributing cause could be found.

**Bladder** The urinary bladder was normal.

**Internal Genitalia** There was hemorrhage in the endometrium and also in the vaginal mucosa.

**Bone Marrow** The vertebral marrow was red and appeared to be normal. Owing to restriction of the autopsy no marrow was taken from the femur.

*Microscopic Postmortem Examination*—**Lungs** Sections of the upper lobe of the right lung showed embolic interstitial pneumonia with hyaline thrombi in the capillaries of the alveolar walls and many leukocytes, with an early stage of necrosis and beginning abscess formation. These lesions were entirely vascular and had no relation to the bronchi. A section of the left lung shows a solitary abscess in an early stage, with surrounding emphysema. There was moderate sclerosis of the arteries and arterioles.

**Gastro-Intestinal Tract** The mucosa of the stomach was atrophic. Sections of the jejunum and ileum showed inflammatory nodules in the submucosa. These inflammatory foci were composed of a vascular fibrous stroma, lymphocytes, plasma cells, large mononuclear phagocytes and a few polymorphonuclear leukocytes. The mucosa was intact over many of these nodules, but there was ulceration over others. Regardless of whether the mucosa was ulcerated or not, a striking feature was the inflammation of the blood vessels, both arterioles and veins, in these nodules. Some of the vessels showed an early stage of thrombosis and polymorphonuclear leukocytes in the wall, and a few could be definitely associated with small pustules. Few polymorphonuclear leukocytes were seen except in connection with these vascular lesions or on the surface of the ulcers. Many lymphatic vessels contained large mononuclear phagocytic cells. In a few instances the lymphocytes, plasma cells and large mononuclear cells were invading the muscularis and even extended into the subserosa.

**Liver** There were cholangitis characterized by infiltration of round cells, a few large mononuclear phagocytes and only an occasional polymorphonuclear leukocyte about the portal triads. Many focal areas of necrosis were present, particularly in the region of the central vein. These foci of necrosis contained many large mononuclear cells but only a few polymorphonuclear leukocytes.

**Gallbladder** The submucosa and the muscularis were distended by edema and infiltration of round cells, large mononuclear cells and polymorphonuclear leukocytes. There were foci of necrosis which had a definite relation to blood vessels. Several small vessels showed an early stage of thrombosis and some inflammation. The mucosa was intact. There was much fibrosis in the subserosa, with slight round cell infiltration.

**Spleen** Many sinusoids and a few vessels contained hyaline thrombi. There was congestion of the sinusoids with red blood cells and conspicuously large numbers of plasma cells, which were abundant also in the pulp. There was hyaline-

tion in several of the malpighian bodies. A few eosinophilic and neutrophilic myelocytes were present. There were also a few megakaryocytes and normoblasts. Several milium abscesses were present in the pulp. These showed leukocytic infiltration and fragmentation of the nuclei and were surrounded by a zone of hemorrhage. Many phagocytic cells contained hemosiderin pigment. There was slight arteriolar sclerosis.

**Kidney** There was extensive parenchymatous degeneration of the convoluted tubules, with desquamation of the epithelium and in some instances epithelial regeneration. Many foci of lymphocytes, plasma cells and large mononuclear cells were present in the interstitial tissue of the cortex and medulla. There was hemorrhage about the pelvis. A few lymphocytes, plasma cells and polymorphonuclear leukocytes and rare myelocytes were present in the peripelvic tissue. The glomeruli were normal.

**Bladder** There was hemorrhage into the mucosa.

**Bone Marrow** The vertebral bone marrow was hyperplastic, but few adult polymorphonuclear cells were present. A few myelocytes and myeloblasts were seen, and there were many megakaryocytes and normoblasts. The predominating cells were the large mononuclear phagocytes. There were scattered plasma cells and lymphocytes, with some foci of the latter. In addition to this chronic inflammatory process, there were many small focal areas of acute necrosis, with a concentration in them of polymorphonuclear cells and mononuclear phagocytes.

The essential features in this case were the anemia, the intestinal ulcers, the focal necrosis in the spleen, bone marrow and liver, the cholecystitis, the cholangitis, the pneumonitis and the interstitial nephritis.

A gram-negative capsule-forming bacillus was recovered from the bile and the intestinal ulcers which seemed to belong to the *Bacillus mucosus-capsulatus* group. This organism was capable of reproducing similar lesions in the monkey (*Macaca mulatta*). The source and portal of entry of the organism into the body were obscure.

#### BACTERIOLOGY

Cultures of material from the ulcers in the small intestine and from the bile revealed a gram-negative bacillus which was small but which varied slightly in length. It grew abundantly on ordinary mediums. On plain agar the colonies were entire, glistening, convex and mucoid. In infusion broth the abundant growth gave a turbid appearance, a ring was formed at the top and there was sediment. Gas formed in ordinary infusion broth. The micro-organism grew anaerobically with the production of gas. It was nonmotile. Capsules were formed after incubation for from twenty-four to forty-eight hours in infusion broth. The organism was nonhemolytic.

The organism fermented mannitol, xylose, dextrose, maltose, levulose, inositol, lactose, sucrose and rhamnose, all with the production of gas. It did not ferment dulcitol. There was no formation of indole in peptone water.



*Serology*—Fortunately a sufficient amount of the patient's serum was saved for the following agglutinations

		Titer
Patient's serum against	Unknown organism from ulcer in patient's ileum	1 2,560
	Unknown organism from ulcer in patient's ileum after several transfers in infusion broth	1 20,480
	Unknown organism from patient's bile	1 20,480
	Stock strain of <i>B typhosus</i>	No agglutination
	Stock strain of <i>B paratyphosus A</i>	1 20
	Stock strain of <i>B paratyphosus B</i>	No agglutination
	Stock strain of <i>Bacillus lactis aerogenes</i>	1 80

From this tabulation it is appaient that serologically unknown organisms obtained from the bile and from the ulcers in the small intestine of the patient were identical Furthermore, there seemed to be no serologic relationship between this unidentified bacillus and members of the typhoid group or *B lactis-aerogenes*

In order to determine whether the serums of average persons possess any agglutinins against this organism, the serums of six normal subjects were pooled and used in agglutination experiments

	Titer
Pooled normal serum (human) against unknown organism from ulcer in patient's ileum	1 10

The foregoing data present conclusive serologic evidence not only that the patient harbored the unknown organism but that this organism was active in producing agglutinins, which the average person has only in a small titer or not at all

It was impossible to do further serologic tests with the patient's own serum because of the limited amount available In order to obtain serum for further identification work, rabbits were immunized by subcutaneous inoculations with the unidentified bacillus

Eleven subcutaneous inoculations of 0.5 cc of fresh twenty-four hour infusion broth culture of the unknown organism were given to each rabbit at three day intervals In several cases an abscess developed at the site of the inoculation Ten days after the completion of these inoculations blood was drawn, and the serum was separated for further work on identification In the following tabulation the immunized rabbit serum was used against known stock strains of the listed organisms which seemed most closely related to the unknown organism both morphologically and according to cultural characteristics

		Titer
Serum of rabbit immunized against unknown organism	Unknown organism	1 2 560
	Organism from ulcer in colon of monkey 2	1 2 560
	<i>Bacillus lactis aerogenes</i>	1 80
	<i>Escherichia coli</i>	1 20
	<i>Bacillus proteus X19</i>	1 40
	<i>Bacillus cloacae</i>	1 10
	<i>Bacillus Friedlanderi</i>	No agglutination
	<i>Bacillus Friedlanderi E G S</i>	No agglutination
	<i>Bacillus Friedlanderi K</i>	No agglutination

From this tabulation it is apparent that immunized rabbit serum gave a high titer against the infecting organism but failed to show high titers against the known organisms with which it might possibly be confused by morphologic or cultural characteristics

This organism appeared to be rather closely related to *B. lactis-aerogenes*. However, rabbits immunized against a stock strain of *B. lactis-aerogenes* failed to confirm this relationship.

Serum of rabbit immunized with <i>B. lactis-aerogenes</i> against		Titer
		1 2,560
{	<i>B. lactis aerogenes</i>	No agglutination
	Organism isolated from ulcer in patient's ileum	No agglutination
	Organism from patient's bile	No agglutination
	Organism from ulcer in colon of monkey 2	No agglutination

Thus the serum of rabbits immunized against *B. lactis-aerogenes* agglutinated this organism to the titer of 1 2,560 but failed to agglutinate the unknown bacillus. This is convincing evidence against its being *B. lactis-aerogenes*.

As will be described under animal experimentation, four monkeys were inoculated intravenously with the unknown micro-organism. Two of these (monkeys 1 and 2) came to autopsy, and the bacillus was recovered in each instance from lesions in the intestine. The two other animals (monkeys 3 and 4) lived and their serums showed agglutinations as follows:

		Titer
Serum of monkey 3 infected (66 days) with organism from ulcer in patient's ileum against	{	Same organism 1 20,480
		B lactis aerogenes 1 640
		B Friedlander K 1 5,120
Serum of monkey 4 infected (40 days) with organism from ulcer in patient's ileum against	{	Same organism 1 2,560
		B lactis aerogenes 1 40
		B Friedlander K 1 320

Thus in the monkeys a very high titer developed against the infecting organism, and relatively high titers developed against *B. lactis-aerogenes* and *B. Friedlander* K. These two organisms seemed most closely related to the unknown micro-organism isolated from the patient's bile and the ulcers in the patient's ileum. As a control for these agglutinations, serum of normal monkeys was tested, and it failed to agglutinate the unknown micro-organism or the stock strain of *B. lactis-aerogenes*.

#### ANIMAL EXPERIMENTATION

*Mice*—As little as 0.02 cc. of a twenty-four hour infusion broth culture of the unknown micro-organism killed mice when it was injected intraperitoneally. The mice died of peritonitis and septicemia in from one to three days.

*Rabbits*—Subcutaneous inoculation of the unknown micro-organism produced only a local inflammatory reaction and the development of immunity.

*Monkeys*—**MONKEY 1**—On February 27 3 cc. of a twenty-four hour infusion broth culture of the unknown bacillus (isolated from material from the ulcers in the intestine and from the bile of the patient) was given to this monkey intravenously. The animal passed fresh blood in loose stools on the fourth and fifth days. The diarrhea continued, and the animal died on March 7, the ninth day after the inoculation. Blood counts and determinations of hemoglobin on the fifth day failed to show any significant anemia or other changes in the blood.

The gross lesions of significance were confined to the colon, particularly the cecum and the ascending colon, where there was an acute diffuse inflammatory process, with marked edema and necrosis of the mucosa. No localized ulcers were present. The unknown organism was recovered from the colon.

The significant findings were diffuse colitis with necrosis of the mucosa and thrombosis of some of the vessels in the submucosa. In addition there were minimal cholangitis and marked parenchymatous degeneration of the kidneys, with some hydropic degeneration of the tubular epithelium.

**MONKEY 2**—In an attempt to produce enteritis in this animal after the oral administration of the bacillus, a stomach tube was passed on March 12, and

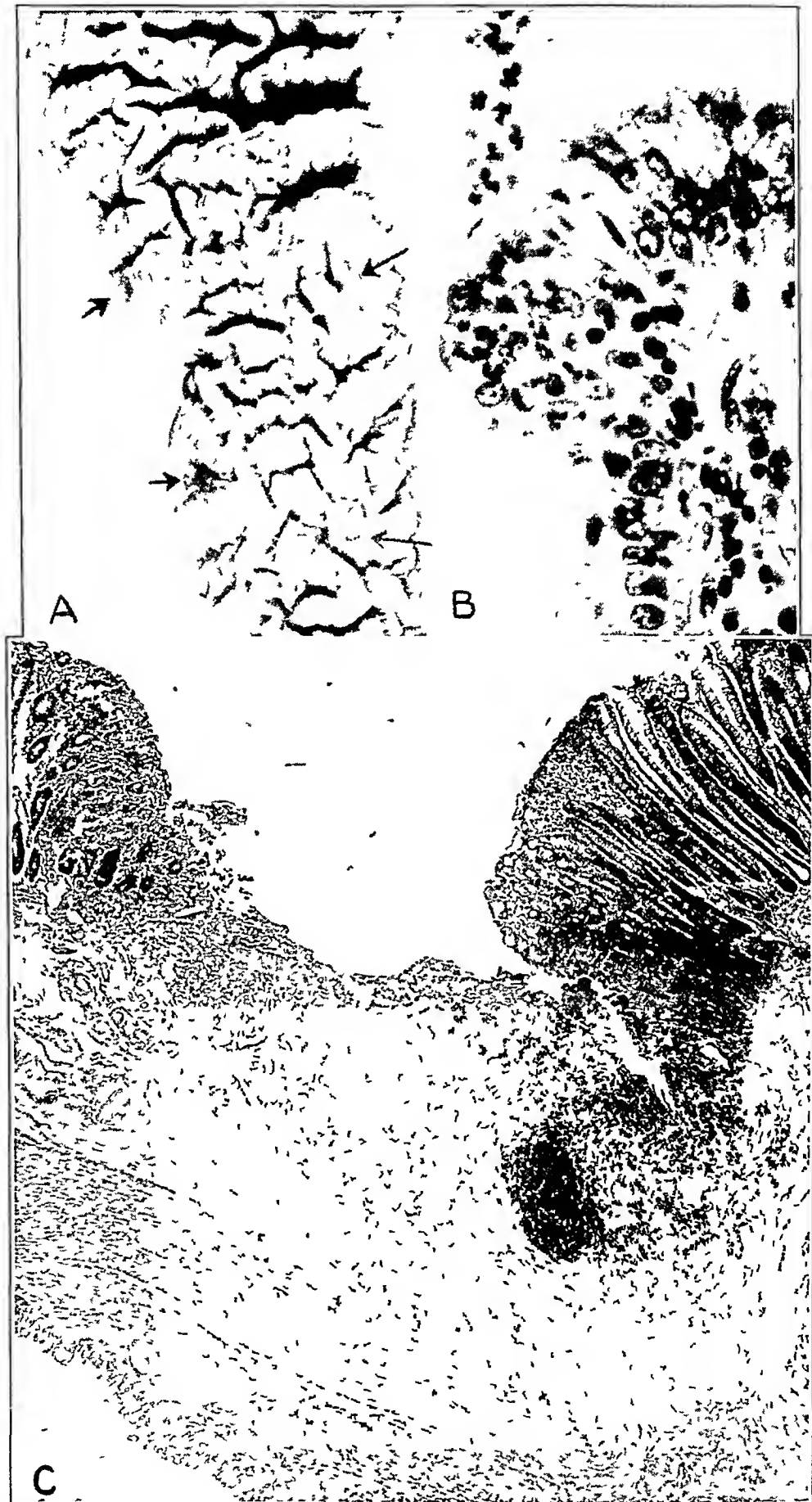


Fig 4—*A*, the ascending colon of monkey 2, showing several well defined ulcers (indicated by arrows) *B*, section of the gallbladder of monkey 2, showing acute inflammation of the mucosa and submucosa,  $\times 475$  *C*, section of an ulcer in the ascending colon of monkey 2, showing an absence of the mucosa and acute and subacute inflammation of the submucosa, with a slight increase in the fibrous tissue near the muscularis,  $\times 44$

4 cc of fresh twenty-four hour infusion broth culture of the original unknown organism was injected into the stomach. There was no diarrhea or suggestive evidence of infection during the succeeding eleven days. On March 23 the animal was given 4 cc of the infusion broth culture of the unknown organism intravenously. Diarrhea developed four days later, but there was no blood in the stools. Thus diarrhea continued, the animal became sick but soon began to improve. On April 4 (the twenty-third day after the intravenous inoculation) it was killed.

There were several small abscesses in the lungs and one in the liver. The entire gastro-intestinal tract was edematous, and there were several small, well defined ulcers in the colon, similar to those noted in the patient's ileum.

The liver showed cholangitis characterized by infiltration by round cells and polymorphonuclear leukocytes about the portal triads. A section taken through the abscess showed in the gross an attempt at encapsulation with a wall of lymphocytes, polymorphonuclear leukocytes and some fibrous tissue. The gallbladder showed edema of the entire wall, with marked cellular infiltration. Many round cells and polymorphonuclear leukocytes were between the muscular layers and in the mucosa. In one area polymorphonuclear leukocytes were passing through the mucosa into the lumen of the gallbladder. The gastro-intestinal tract showed edema throughout. No ulcers were present in the small intestine, but in the colon, in addition to slight infiltration of the mucosa with polymorphonuclear leukocytes, there were well defined ulcers in the mucosa, with marked inflammation even down into the submucosa. On the surface of the ulcers were blue, amorphous clumps of bacteria, and beneath these there was much acute and subacute inflammation, with some increase in the amount of fibrous tissue, particularly deep near the muscularis. The kidney showed focal accumulations of lymphocytes and large mononuclear cells in the interstitial tissue, giving the typical appearance of interstitial nephritis. The tubules showed marked parenchymatous degeneration. The bone marrow showed focal accumulations of leukocytes and petechial hemorrhages, but no significant changes were observed in the myeloblastic or erythroblastic tissues. The spleen was loaded with leukocytes, and the malpighian bodies showed marked hyperplasia with some necrosis. Many phagocytic cells contained hemosiderin pigment.

The blood culture was sterile. The original bacillus was recovered in pure culture from the bile and predominated in cultures of material from the ulcers in the colon of this monkey.

**MONKEY 3**—On March 12 this monkey was given intravenously 3 cc of a twenty-four hour infusion broth culture of the original organism. The animal appeared to be acutely ill for several days, but it recovered without evidence of enteritis. On May 18 blood was drawn for agglutination purposes (see the tabulation in the previous section, on bacteriology).

**MONKEY 4**—In order to determine the amount of anemia produced in this animal, blood counts were made before inoculation with the organism and after an interval of five weeks. On April 8 the blood count showed 6,190,000 erythrocytes, with 14 Gm of hemoglobin. On the same day 35 cc of twenty-four hour infusion broth culture of the organism recovered from the bile of monkey 2 (which was identical with the original organism obtained from the patient) was given intravenously to this monkey. Six days later there was diarrhea without blood, which continued for about five days. On May 13 a blood count showed 4,050,000 erythrocytes, with only 10 Gm of hemoglobin, thus indicating definite

anemia On May 18 blood was drawn for serologic work (see the tabulation in the previous section on bacteriology)

Two attempts to produce the infection in monkeys by subcutaneous injection were unsuccessful, as only localized induration followed

#### COMMENT

The two common types of specific ulceration of the small intestine are (1) that due to *B. typhosus*, characterized by ulceration of Peyer's patches and the solitary follicles and (2) that due to the tubercle bacillus, which, as in typhoid in its earlier stages, is confined to the lymphoid tissue of the small intestine and colon In addition to these, not infrequently the dysentery group of organisms cause lesions in the terminal ileum as well as in the colon

Nonspecific solitary and multiple ulcers have been described in the small intestine Many of these have been called peptic ulcers of the small intestine No etiologic micro-organism has been isolated and proved to be the cause of any of this group of conditions

The ulceration in the case reported here differs from the usual types in the small intestine in two principal ways (1) etiologically, since an unclassified gram-negative capsule-forming bacillus was isolated from the ulcers and from the bile of the patient, and all evidence points to it as the cause of the ulceration, (2) anatomically, since the distribution of the ulcers without definite relation to the lymphoid tissue or to the circumference of the intestine differs from that seen in the ordinary types of enteritis

The ulcers in this case were present in the upper portion of the jejunum, and they increased in number near the ileocecal valve They showed no definite or constant relationship to the lymphoid tissue or the circumference of the intestine Peyer's patches and the solitary follicles were not hyperplastic The ulcers were seen more frequently on the mesenteric than on the antimesenteric side of the lumen The earliest lesions began as inflammatory nodules in the submucosa, with what appeared to be primary involvement of the vessels in this area Later the mucosa over the nodules became necrotic, and ulceration of the mucosa and submucosa resulted

While the enteritis was of primary importance because of its unusual etiologic and anatomic features, the cholecystitis, cholangitis, interstitial nephritis, inflammation of the bone marrow and pneumonia also were of great importance, because they were apparently caused by the same bacillus and undoubtedly contributed greatly to the patient's death

The specific gram-negative bacillus was agglutinated by the patient's own serum in a titer of 1:20,480 Infusion broth cultures when injected intravenously into the monkey reproduced ulcers in the colon similar to those noted in the small intestine of the patient The bacillus

was again isolated from the ulcers in the monkey's colon in almost pure culture and from the bile in pure culture

Cholecystitis, cholangitis, pneumonitis and interstitial nephritis similar to those in the patient were reproduced in the monkey after intravenous inoculation of the unclassified micro-organism

The specific bacillus undoubtedly belongs to the general group of encapsulated gram-negative bacilli with which *B. lactis-aerogenes*, *Bacillus pneumoniae* of Friedlander, *Bacillus acidilactici* and *Bacterium rhinoscleromatis* are associated. Identification of this bacillus is difficult because it does not conform to any of the known strains in all its characteristics. Like *Bacillus lactis-aerogenes* it ferments dextrose, saccharose and lactose, and in this respect may be said to differ from the others, none of which is said to ferment all of these sugars. However, even this is a questionable differentiation, as fermentations are often so variable. Serologically it differs from *B. lactis-aerogenes* and Friedlander's bacillus (see the tabulation in the previous section, on bacteriology). The patient's and the rabbit's serum gave definite evidence of individuality, however, monkey serum was not so conclusive. Thus, morphologically, culturally and serologically this bacillus appears to be a distinctive strain but has not been positively identified, because of the marked variations in the members of this group. However, its pathogenicity certainly places it in a class by itself.

There is some resemblance between this infection and typhoid. Both are marked by leukopenia, an exudate of mononuclear cells in the intestinal ulcers, focal necrosis in the spleen, the bone marrow and the liver and cholecystitis with infection of the bile. However, the type and distribution of the intestinal ulcers and the etiologic organisms in these two diseases are entirely different.

The marked parenchymatous degeneration and especially the interstitial nephritis are evidences of intoxication. The interstitial nephritis is similar to but more severe than that in such infectious diseases as scarlet fever and diphtheria.

The question of antecedent pernicious anemia is pertinent. The color index of 1.3 and absence of free hydrochloric acid in the stomach strongly suggest such a possibility, but the absence of a striking variation in the size, shape and staining characteristics of the red blood cells is against this assumption. The anemia might have been due to loss of blood in the intestine, intoxication and necrosis of bone marrow resulting from the specific infection.

In the absence of any illuminating evidence in the history which might suggest the source and mode of infection, no conclusive pathologic observations throw light on these important points. However, the vascular lesions in the intestine, gallbladder and lung, along with

the interstitial nephritis and the inflammation of the bone marrow and spleen, suggest that the organism was blood borne. Although cultures of the blood made four days before death and at the time of autopsy were sterile, it is entirely possible that the unknown organism had been present in the blood earlier in the disease.

The patient's history of an insect bite on the foot a week before she became ill suggested the possibility that the bacillus gained entrance through the skin. In following this lead, subcutaneous inoculation of the organism in monkeys and rabbits failed to show more than a localized response and the development of immune bodies. Monkeys given the bacillus by mouth (stomach tube) failed to show any evidence of enteritis or infection.

#### SUMMARY

A report is made of a peculiar case of ulceration of the small intestine in which there were cholangitis, cholecystitis, interstitial nephritis, pneumonitis and inflammation and necrosis of the bone marrow.

A gram-negative capsule-forming bacillus was isolated from the intestine and from the bile which was capable of reproducing similar lesions in the monkey (*Macaca mulatta*).

This unclassified specific bacillus is possibly related to the *B. mucosus-capsulatus* and *B. lactis-aerogenes* groups, although it is immunologically distinct.

# CLINICAL ASPECTS OF PERIARTERITIS NODOSA

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In the sixty-five years since periarteritis nodosa was presented as a disease entity by Kussmaul and Maier, the accrued pathologic and clinical material has helped to clarify the conception of its symptomatology and pathogenesis. First considered solely as a medical curiosity, periarteritis nodosa now is known to be of significance in relation to certain other syndromes which, though more familiar, are none the less still obscure.

In the classic case of Kussmaul and Maier<sup>1</sup> the condition was at first considered clinically to be trichiniasis. These observers, therefore, regarded the diagnosis of periarteritis nodosa as possible if symptoms suggesting trichiniasis occurred in association with nephritis and enteritis and if biopsy of a muscle nodule showed pericapillary cellular infiltration but no trichinas. Since then, however, every discussion has emphasized the protean manifestations and the rarity of a correct diagnosis during life. P. S. Meyer (1878) suggested as the diagnostic formula of periarteritis nodosa the triad of "chlorotic marasmus," polymyositis and polyneuritis, and gastro-intestinal symptoms.

Successive observers recognized the wider clinical range of this malady. Thus Harbitz<sup>2</sup> in 1927 distinguished six types—gastro-intestinal, renal, neuromuscular, cardiac, cerebral and cutaneous. Singer<sup>3</sup> made the following more comprehensive statement:

The bewildering symptomatology of the disease can be rendered least intricate by assuming the presence of an infectious process which, in addition to producing general disturbances such as fever, tachycardia, prostration, cutaneous eruptions and leukocytosis, causes symptoms based on circulatory disturbances in the systems or regions affected.

From Singer's summary it is apparent that almost innumerable combinations of symptoms involving different systems are possible and even predictable, indeed, new ones are reported frequently.

From the Mount Sinai Hospital

1 Kussmaul, A., and Maier, R. Ueber eine bisher nicht beschriebene eigenthumliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellahmung einhergeht, *Deutsches Arch f klin Med* **1** 484, 1866.

2 Harbitz, F. Different Forms of Arteritis, Especially "Periarteritis Nodosa," *Internat Clin* **3** 130, 1927.

3 Singer, H. Periarteritis Nodosa, with Special Reference to the Acute Abdominal Manifestations. Report of Two Cases, *Arch Int Med* **39** 865 (June) 1927.



This sketch of the syndrome is not complete without emphasis on one real though intangible clinical characteristic—the disproportion between the number and intensity of the symptoms and the disease which is assumed to be their cause, thus the diagnosis that is made generally seems a little strained and not quite apt. Because of the variability in the occurrence of symptoms, periarteritis nodosa has mimicked other conditions and, even with the aid of biopsies, has been diagnosed correctly in only about 12 per cent of the reported proved cases. However, in very recent years diagnoses have been much more accurate.

#### SUMMARY OF THE PATHOLOGIC OBSERVATIONS

The pathologic condition to which the syndrome owes its name is the picturesque appearance of gross aneurysmal dilatations of the arteries. This, however, has been mentioned in only a minority of the cases and is not the essential characteristic. The pathologic pattern is a primary injury to the wall of the vessel with swelling, necrosis and fibrillation of the media, destruction of the elastica interna and infiltration of the adventitia with polymorphonuclear leukocytes, which are often eosinophilic, and also with many histiocytes.

A variety of vascular lesions may occur secondary to this initial lesion, for instance, aneurysms at the site of weakening of the vessel wall, hemorrhages or thromboses, with a train of symptoms based on these mechanical complications. Tendencies to healing occur, as manifested by fibrosis of the involved vessels or recanalization of thrombosed vessels. However, this histologic healing frequently results in clinical disease, since there is injury to tissues and organs due to local nutritional changes. Manges and Baehr<sup>4</sup> studied a case in which successive biopsies were made of affected vessels at three stages during the clinical course. They demonstrated that the degenerative lesions of the vessel walls seen in some of the previously reported cases were the late "healed" sequelae of an earlier acute inflammatory process.

These vascular changes are most extensive on the arterial side of the circulation and, more specifically, of the medium-sized arteries, including the vasa vasorum of large arteries. Veins also are involved but to a remarkably less extent in respect to the rapidity of development of the process, the severity of the lesion and the number of involved vessels. Capillary injury, such as occurred in the muscle in the case reported by Kussmaul and Maier, produces various symptoms and may be manifested by purpura and urticaria. The vascular lesions are most frequently generalized, though some instances have been reported in

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<sup>4</sup> Manges, M., and Baehr, G. Periarteritis Nodosa, *Am J M Sc* **162** 162 (Aug) 1921

which they were limited to one or a few organs (Fishberg<sup>5</sup>) One may surmise that many such lesions occur but escape clinical notice Besides these vascular lesions, granulomatous nodules of the serosal membranes have been noted occasionally

The tempo of the course may be acute, subacute or chronic Manges and Baehr called attention to the fact that both acute and healing lesions may be present in the same case Though the name denotes vascular involvement, parenchymatous degeneration of tissue occurs which is not directly dependent on local arterial lesions

Periarteritis nodosa is not restricted to the human species<sup>6</sup> An epidemic infectious disease among deer and also among swine has been noted in which similar lesions were present This fact suggested that these species might be the reservoir of an unknown virus, a relation similar to that of lower animals and the virus of typhus fever

Opinions as to etiologic factors have reflected changing medical concepts, and only recently has any suggestive experimental evidence been adduced Because the periarteritic nodules were proved to be aneurysms, the cause, particularly in pre-Wassermann-test days, was attributed to syphilis The patient reported on by Chvostek and Weichselbaum<sup>7</sup> (1877) had encephalitic symptoms, including disturbed pupillary reflexes On the basis of these clinical findings and the resemblance between the periarteritic lesions and the perivascular lesions of syphilis, a common cause for the two conditions was assumed In the case reported by Schmorl<sup>8</sup> (1903) the diagnosis of periarteritis nodosa was established by biopsy in a woman aged 53, and antisiphilic therapy was instituted When the patient died, two years later, of acute thrombosis of the portal vein, widely distributed healed lesions of periarteritis nodosa were observed Syphilis was assumed to be the cause, owing to the so-called therapeutic test This observation is not of etiologic significance, since lesions of periarteritis nodosa may heal spontaneously Of 30 recent cases of periarteritis nodosa, Gruber<sup>9</sup> cited a history of syphilis in 3 and a positive Wassermann reaction in 2 Spirochetes have never been demonstrated in the tissues in a case of undisputed periarteritis nodosa On evidence of this kind it appears that the relationship between syphilis and periarteritis nodosa is certainly not unusually close

5 Fishberg, A Zur Kenntnis der Periarteritis nodosa insbesondere der Histiopathogenese, *Virchows Arch f path Anat* **240** 483, 1923

6 Joest, E, and Harzer, J Ueber Periarteritis nodosa beim Schwein, *Beitr z path Anat u z allg Path* **69** 85, 1921

7 Chvostek and Weichselbaum Herdweise syphilitische Endarteritis mit Aneurysmenbildung, *Allg Wien med Ztg* **22** 257, 275 and 294, 1877

8 Schmorl, cited by Gruber,<sup>9</sup> *Verhandl d deutsch path Gesellsch* **6** 203, 1903

9 Gruber, G B Zur Frage der Periarteritis nodosa, *Virchows Arch f path Anat* **258** 441, 1925

Eppinger<sup>10</sup> suggested an intrinsic weakness of the vascular system as the essential predisposing factor (1887) Dietrich<sup>11</sup> suggested that a reflex nervous involvement of the vascular wall is the underlying mechanism (1933)

The syndrome has been considered also a specific infectious disease Attempts to reproduce the disease in lower animals by inoculation of crushed nodules and subinoculation have been inconclusive (Harris and Friedreich<sup>12</sup>) Klotz<sup>13</sup> in 1917 claimed to have initiated the essential lesions of the disease in rabbits by means of injections of streptococci, but aneurysms and thromboses were absent Metz in 1931 produced lesions of a periarteritic type but without aneurysms in rats The animals were first highly sensitized to streptococci, and then either these organisms or nonspecific serum was injected This experimental work is in accord with Gruber's conception of periarteritis nodosa as a peculiar hyperergic expression of the sensitized portions of the arterial walls of one or several organs in the course of some prolonged infection or septic disease

The standard clinical features have been well described by a number of writers A miscellany of additional variations in symptomatology will be presented here from a series of cases of proved periarteritis nodosa studied at the Mount Sinai Hospital in the last fifteen years,<sup>14</sup> and also 2 from the St Vincent's Hospital, of Staten Island, New York<sup>15</sup> The case histories are given in detail, but the summary which follows each report is sufficient for reference purposes

#### REPORT OF CASES

CASE 1—A M, a Mexican aged 33, gave a history of gonorrhea, repeated sore throats and alcoholic sprees One month before his admission to the hospital, on March 11, 1931, severe tonsillitis and cervical adenitis developed and lasted for a week After a brief asymptomatic interval rapidly migratory articular pains and swellings associated with a fine purpuric eruption appeared The following week he had diffuse abdominal pain and persistent constipation The temperature ranged about 103 F Abdominal pain was not entirely new, having been associated with drinking bouts

At the initial examination the patient lay guardedly, complaining of pain in the hypogastrium, knees and hips The heart showed slight enlargement, an apical systolic murmur with diffusion over the left precordial region, a ringing second pulmonary sound, blurred sounds and a suggestion of a pericardial friction

10 Eppinger, cited by Gruber<sup>9</sup>

11 Dietrich, K "Periarteritis Nodosa" der Haut des Vorderarmes nach Erysipelen derselben, *Ztschr f Kreislaufforsch* **25** 305, 1933

12 Harris and Friedreich, cited by Gruber<sup>9</sup>

13 Klotz, O Periarteritis Nodosa, *J M Research* **37** 1, 1917

14 Some of the necropsy material has been reported in other papers from the hospital in different connections (cases 1, 5, 6, 8, 10, 11 and 17)

15 Dr Margot Freund gave permission for the use of these case reports

rub The distention was severe, the hypogastric pain was inconstant and the tenderness was relatively slight Effusion and tenderness of the knee joints were noted A slightly raised, finely purpuric rash with barely perceptible erythematous papulomacules was distributed over the flexor surface of the thighs, insteps, lower costal margin on the right side posteriorly and right buttock

At this time the blood pressure was 140 systolic and 74 diastolic The blood count showed hemoglobin, 86 per cent, leukocytes, 17,000, polymorphonuclear leukocytes, 90 per cent, and platelets, 480,000 The urine contained albumin, red blood cells and casts There was no occult blood in the stools

The initial diagnosis was erythema, with visceral, rheumatoid and perhaps cardiac manifestations

Because of severe constipation, abdominal cramps and distention, an acute surgical abdominal condition was considered to exist, perhaps due to a gangrenous appendix At operation retroperitoneal edema of the appendical bed and partial obliteration of the appendix were present, they were thought insufficient to account for the antecedent clinical course Microscopic examination showed multiple foci of necrotizing arteritis in all phases and subacute inflammation of the appendical wall The diagnosis of periarteritis nodosa was thus established by operation, and further manifestations were awaited

The subsequent course was characterized by persistent distention, ileus, remittent fever and inanition The urea nitrogen content of the blood fluctuated about 50 mg per hundred cubic centimeters The urinary findings remained unchanged The blood pressure rose in one month to the level of 160 systolic and 110 diastolic The hemoglobin content decreased to about 50 per cent, and the leukocytosis rose to 36,000 Pitting edema of the feet gradually appeared Fleeting precordial pain, vagrant cardiac murmurs and also a transient tripartite rhythm, which was considered equivalent to a pericardial friction rub, were noted Nodules were not detected in the peripheral blood vessels The electrocardiogram was normal Roentgenographic examination showed pneumonia of the lobular type in the lower lobe of the right lung Death occurred about three months after the onset of tonsillitis

*Postmortem Observations*—The patient died on May 18 Examination revealed macroscopic periarteritis nodosa of the bronchial, coronary, pancreatic, mesenteric, adrenal and cystic arteries, brown induration of the lungs with submiliary nodules and thrombosis without infarction, fibrinous pericarditis, verrucae of the closure line of the mitral valve, hemorrhagic infarctions of the liver associated with obliteration of the arteries, and diffuse gliosis of the brain

Microscopically there were hyalinization and occasional intimal proliferation of the cerebral arteries, myocardial degeneration, with Aschoff bodies, subacute glomerulonephritis of the intracapillary type, small renal aneurysms, and productive thickening of the meninges

*Summary*—Clinically this patient's condition belonged to the Osler erythema or the Schonlein-Henoch group with abdominal symptoms, for which appendectomy was performed The lumen of the appendix was obliterated, characteristic lesions of periarteritis nodosa were noted microscopically The subsequent course was complicated by pericarditis, pulmonary symptoms, renal insufficiency, hypertension, fever and progressive inanition The postmortem examination showed periarteritic involvement of the lungs, heart, liver, gallbladder and kidneys, fibrinous pericarditis and subacute glomerulonephritis

CASE 2—A 6 year old boy was admitted to St Vincent's Hospital without a previous history of significant illness. The child had had severe abdominal pain for two days without vomiting. The abdomen was diffusely rigid, a systolic murmur was present and the temperature was 102 F. The leukocyte count was 28,000 with 80 per cent polymorphonuclears and rose in two days to 39,000 with 96 per cent polymorphonuclears. Appendectomy was performed, and the lesions of periarteritis nodosa were revealed. Recovery was uneventful.

*Summary*—A child with abdominal pain and rigidity, fever and leukocytosis was operated on for appendicitis. Periarteritis nodosa involving the appendix was demonstrated.

CASE 3—H. B., a 17 year old Jewess, was admitted to the hospital on May 23, 1932. She had apparently been well but for one year of intermittent pain in the right lower quadrant of the abdomen, which was exaggerated only by exertion. Some tenderness on deep pressure over McBurney's point was present. A short presystolic murmur was noted at the apex, with marked reduplication and accentuation of the second pulmonic sound. Laboratory examination revealed no abnormality. A pyelogram showed slight dilatation of the pelvis of the left kidney and some mobility of the right kidney. Nephropexy and appendectomy were performed on the right side, the cecum was congested and the appendix shriveled. Histologic examination of the appendix showed chronic inflammation, with obliteration of the lumen, and many arterioles, with acute necrotizing arteritis as in periarteritis nodosa. On close questioning postoperatively a history of fleeting articular pain was elicited. The convalescence was uneventful except for mild pharyngitis. The patient was discharged from the hospital on June 16. Follow-up examination has shown no subsequent symptoms.

*Summary*—A girl, otherwise apparently well, had atypical pain in the right lower quadrant of the abdomen, for which appendectomy and right nephropexy were performed. Necrotizing arteriolitis of the appendix was present. The patient is now apparently well.

CASE 4—An 8 year old Irish boy was admitted to St Vincent's Hospital. Nausea, vomiting and abdominal pain had developed three days before, and a diagnosis of appendicitis was made. There was a leukocyte count of 20,000 with 86 per cent polymorphonuclear cells, together with acetoneuria. Appendectomy was performed on the same day, the appendix was normal.

Three days later the boy had several convulsions and then complained continuously of pain in the abdomen and in both arms. White blisters appeared on the tongue.

Two blood transfusions were given, and six weeks after admission to the hospital the boy seemed well enough to be out of bed. Transient amaurosis and vagrant pains occurred repeatedly. His face became swollen. The urine contained increasing amounts of albumin, casts and red and white blood cells. No note was made of the blood pressure. The temperature range was from 98 to 103 F. Reddish fluid oozed from the rectum the day of his death.

The postmortem examination showed periarteritis nodosa of the mesenteric arteries, renal arterioles and hepatic arteries in various stages of healing, adhesions in the right pleura, leukocytic infiltrations of the lung without arterial changes, cardiac enlargement, thickening of the anterior cusp of the mitral valve, slight fibrosis of the papillary muscle, mitral proliferation of the coronary artery, organizing necrosis of the myocardium, fatty degeneration of the liver,

aneurysm of an artery of the jejunum, with ulceration, and hyalinization of collapsed glomeruli. The general nervous system was not examined.

*Summary*—A boy with symptoms interpreted as due to appendicitis was operated on. During convalescence convulsions, transient amaurosis, albuminous urine and sanguineous stools were noted. Hemorrhage from an aneurysm in the jejunum, chronic peritonitis and pleurisy, acute glomerulonephritis and periarteritis nodosa were noted at necropsy.

CASE 5—Y S, a 10 year old Jewess, was admitted to the hospital on June 12, 1924. Three weeks before her admission to the hospital the patient had a sore throat and fever followed by pain and swelling in the right ankle. Two weeks later she had diffuse abdominal cramps and vomited. She was sent to the hospital because of a suspicion of acute appendicitis. On the day of admission to the hospital she fainted and was amaurotic. The temperature at that time was 102 F, and the blood pressure was 180 systolic and 124 diastolic, persisting at this level for most of the clinical course. Purpura of the left hip, fundal hemorrhages, perivasculitis of the retina, nuchal rigidity and a Kernig sign were present.

The hemoglobin value was 93 per cent, the initial leukocyte count was 40,000 with 90 per cent polymorphonuclear cells, subsequently it became 12,000. The urine contained albumin, casts and red and white blood cells. The spinal fluid was normal. The terminal urea nitrogen content of the blood was 30 mg per hundred cubic centimeters.

There were occasional convulsions, and consciousness varied so that at times the patient apparently perceived objects. On June 23 the blood pressure fell, and death occurred.

The diagnosis rested between uremia and encephalitis.

Postmortem examination showed fatty replacement of the thymus, marked enlargement of the intertracheal lymph nodes and moderate hypertrophy of the left ventricle. Along the course of the coronary arteries were glairy, light brown masses connected with the lumen of the vessel. The greater omentum was attached to the intestine by fibrinopurulent exudate. Two irregular ulcers in the small intestine and numerous aneurysms of the mesenteric vessels were noted. No gross aneurysm of the kidneys but numerous yellow wedge-shaped infarctions, corresponding to microscopic occlusions, of the renal arterial supply by periarteritic lesions were present.

*Summary*—Following arthritis and an infection of the upper respiratory tract, abdominal symptoms suggestive of acute appendicitis appeared. Soon transient amaurosis, hypertension and symptoms of involvement of the central nervous system developed. At postmortem examination periarteritis nodosa and fibrinopurulent peritonitis were present.

CASE 6—W S, a 39 year old Jew, was admitted to the hospital on Sept 3, 1919. He gave a history of typhus fever and recurrent peritonsillar abscesses. The illness under consideration began with pains in the muscles of the legs, in the right testicle and in the lumbar region. On one occasion hematuria, epigastric pain and fever simulating an acute surgical condition occurred. Vague epigastric tenderness was noted. There was marked inflammation of the tonsils.

The temperature ranged about 102 F. The pain subsided and the leukocyte count varied between 36,000 and 54,000 with 75 per cent polymorphonuclear

cells The blood pressure was 160 systolic and 90 diastolic The urea nitrogen content was 35 mg per hundred cubic centimeters of blood

A pure culture of *Streptococcus haemolyticus* was obtained from material from the throat

All diagnostic approaches having given negative information, the patient was considered to have suppurative retroperitoneal foci behind the omental sac secondary to the pharyngeal infection

At exploratory laparotomy periarteritis nodosa of the mesenteric vessels, enlargement of the head of the pancreas and an area of fat necrosis in the omentum were noted Peritoneal cultures were sterile

Five days postoperatively there was painless hematuria A diffuse maculopapular rash on the hands and forearms and external nodules appeared The nodules on the face were pulsatile Failing vision and a fibrinous exudate on the temporal side of the optic nerve head were noted and a low grade of nephritis

The patient was discharged slightly improved but was readmitted in two months with generalized edema, dyspnea, urinary signs of nephritis and patchy consolidation of the lungs The sputum contained pneumococci and streptococci

All the nodules had disappeared except several hard ones along the temporal and brachial arteries There was neuroretinitis, and the blood pressure was 104 systolic and 100 diastolic Bronchopneumonia and uremia developed Death occurred on October 8

Postmortem examination revealed periarteritis nodosa and aneurysms of the temporal, brachial, coronary, splenic, gastric, renal, pancreatic and superior mesenteric arteries, thickening of the pleurae at the apexes, lobular pneumonia and anthracosis, hemorrhage in the pericardial sac, congestion of the gastric mucosa, four shallow gastric ulcers on the posterior aspect near the lesser curvature, with hemorrhage extending down to the muscularis, pancreatitis, and perirenal hematoma and perinephritis No changes were noted in the brain

*Summary*—The patient had myalgias, followed by severe abdominal pain and hematuria, for which an exploratory laparotomy was performed The diagnosis of periarteritis nodosa was made at that time Subsequently, painless hematuria, large subcutaneous perivascular nodules and a maculopapular rash on the upper extremities appeared Death occurred, with uremia, in two months A perirenal hematoma, gastric ulcers and pancreatitis, in addition to the characteristic vascular lesions, were present

CASE 7—M B, a 38 year old Jew, was admitted to the hospital on Dec 23, 1931 He had passed a life insurance examination three years before and had had no acute infectious illnesses Pleural pain developed on the right side a year and a half later, and subsequently there were headaches, dyspnea and nocturia At this time hypertension was discovered The symptoms increased, and edema of the ankles appeared At the time of his admission to the hospital examination of the fundi showed obliterated disk margins, reddened disks, extremely thin arteries, full veins, many exudates and a few hemorrhages Râles were present at the bases of the lungs, the heart was enlarged to the left and a gallop rhythm was present The liver was enlarged, and ascites was present

The blood pressure was 205 systolic and 150 diastolic The hemoglobin value was 85 per cent The leukocyte count was 35,000 with 86 per cent polymorphonuclear cells The venous pressure was 22 cm of water An electrocardio-

gram showed left ventricular preponderance, an inverted  $T_1$  wave and low  $T_2$  and  $T_3$  waves, suggestive of poor myocardial function. The urea nitrogen content was 34 mg per hundred cubic centimeters of blood. The initial examination showed much albumin and some casts in the urine. The diagnosis at that time was the malignant phase of essential hypertension.

Irregular, low grade fever was present and was attributed to bronchopneumonia, probably at the base of the left lung. No roentgen findings were recorded.

Two weeks after admission to the hospital the patient became stuporous and cyanotic and had Cheyne-Stokes respiration. The venous pressure was 14 cm of water. The urine then contained many red blood cells (a transient finding). Swelling and pain were noted on motion of the right knee. The abdomen remained distended. There was tenderness, particularly in the left lower quadrant of the abdomen. The stools were normal. Sepsis due to pneumococci, with metastases to the knee and peritoneum, was considered to be present, but a blood culture was sterile. Aspiration of the knee and abdomen yielded sterile fluid containing 7,000 white blood cells. The leukocyte count at this time was 16,650 with 81 per cent polymorphonuclear cells.

A pericardial friction rub was present. The neck became rigid, and positive Kernig and Brudzinski signs appeared, but the spinal fluid was normal on two examinations. All symptoms continued unchanged, and severe terminal diarrhea developed. The patient died on Jan 16, 1932.

Postmortem examination revealed purpura of the antecubital fossa, cardiac enlargement, a necrotic infarct of the lower lobe of the left lung, with fibrinous pleurisy dependent on a fibrosed blood vessel, healed apical tuberculosis of the upper lobe of the left lung, bronchopneumonia of the lower lobes of both lungs, pleural adhesions on the left, fecal peritonitis, hemorrhagic infarcts of the small intestine, with one perforation in the jejunum, small punctate purpuric, occasionally ulcerated lesions of the mucosa of the large intestine, infarcts of the liver and pancreas secondary to fibrosed or necrotic arterioles, finely granular kidneys, mottled by tiny confluent depressed punctate red areas, necrotizing ureteritis, and edema of the brain.

Microscopically, necrotizing arteritis of the small coronary branches and a large parietal thrombus of one coronary artery were noted. The outstanding lesion in the kidneys was the severe intimal thickening of the entire arterial tree, which was loosely cellular and without much hyalinization. The renal parenchyma showed focal atrophy with an increased amount of stroma and vascularization and frequent fibrotic glomeruli without capsular exudate or an increased number of nuclei. The renal picture was that of nephrosclerosis lenta progressa. There was thickening of the cerebral vessels with perivascular gutter cells and diffuse gliosis.

*Summary*—After hypertension, neuroretinitis and cardiac insufficiency of about a year's duration the patient showed nuchal rigidity, bloody urine, diarrhea, swelling of the right knee and abdominal tenderness. Clinically he appeared to suffer from malignant sclerosis. At necropsy, in addition to malignant nephrosclerosis, periarteritis nodosa was present, with secondary ulcerations of the small intestine, hepatic infarcts and necrotizing ureteritis.

CASE 8—A V, a 10 year old Jewess, was admitted to the hospital on Feb 27, 1931. Seven weeks before her admission to the hospital the child had mild, atypical scarlet fever, after which desquamation was profuse. A Dick test was



negative The next week urticaria developed and persisted for about a month, accompanied with a temperature ranging up to 104.4 F During this time she complained occasionally of articular pains, especially in the small joints of the hand

The urine was normal, except on one occasion, when a great deal of albumin was present for only one day The blood count and electrocardiogram were normal The blood culture was sterile

Generalized violent abdominal pain and rigidity developed three days before the patient's admission to the hospital Tenderness was especially marked over the right upper quadrant of the abdomen The leukocyte count then was 14,000, with 79 per cent polymorphonuclear cells Exploratory laparotomy was performed for an intra-abdominal suppurative condition There was marked intestinal distention The appendix was normal A fine, fibrinous exudate extended across the under-surface of the liver The gastrohepatic ligament was edematous throughout its entire length, and there were many fine periduodenal adhesions There was no pus

Three days postoperatively bilateral bronchopneumonia developed, involving chiefly the lower lobe of the right lung The leukocyte count ranged about 25,000 with 80 per cent polymorphonuclear cells, the platelet counts were 450,000 and 380,000 There was mild progressive anemia

In spite of several transfusions the child's condition remained poor, and the temperature was unchanged About three weeks after her admission to the hospital a coarse pleural friction rub was noted in the lower portion of the left axilla, and that area became tender and dull The condition remained unchanged for about ten days The liver and subphrenic space were explored by means of aspiration without revealing any positive signs

During this time a distinct, loud systolic murmur had appeared, which varied in intensity and was transmitted toward the axilla There were also occasional transitory murmurs at the base It was concluded that a pericardial effusion might be present Large doses of salicylates were given The temperature was depressed for a few days, but the child became almost pulseless When the salicylates were stopped, the condition of the pulse improved temporarily The child died of heart failure on April 19 Postmortem examination revealed marked pulmonary congestion, acute verrucous lesions of the mitral valve, moderate cardiac enlargement, fresh Aschoff bodies, a complicating lesion of one of the myocardial arteries—disappearance of the elastica interna, fibrosis of the media, marked thickening of the intima and perivascular fibrosis, renal infarcts dependent on periarteritis nodosa of the interlobular arteries, diffusely distributed purpuric spots on the visceral pleura, the peritoneal covering of the entire gastro-intestinal tract and the mesentery, and pleural, perihepatic and perisplenic adhesions

*Summary*—The patient presented the sequence of atypical scarlet fever, urticaria and articular pains and finally showed symptoms suggesting intra-abdominal suppuration within a period of two months At laparotomy the only abnormalities were edema of the gastrohepatic ligament and adjacent fresh adhesions Fever persisted, and a systolic murmur and pericardial friction rub developed There was no response to salicylate therapy Death was due to heart failure Postmortem examination showed lesions of rheumatic fever, periarteritis nodosa of the kidneys and polyserositis

CASE 9—H L, a 50 year old Jew, was admitted to the hospital on Aug 25, 1930 Three months before his admission violent epigastric pain had developed, attributed to ulcer or cholecystitis, and had lasted for ten days The patient had stuttering speech for one day Pain in one leg, nocturia, polydipsia and repeated vomiting then occurred and lasted for about three weeks On the day of admission to the hospital the patient had a sudden, violent headache, followed by sudden complete blindness, gradually the pupils were fixed to light, and left external strabismus and edema of the retina and disk were present Pretibial edema and occasionally a pericardial friction rub were noted

The blood pressure was maintained at about 190 systolic and 120 diastolic The hemoglobin content was 66 per cent The leukocyte count was 12,000 with 94 per cent polymorphonuclear cells The urine contained much albumin and no red blood cells This finding was considered indicative of glomerulonephritis rather than the malignant phase of essential hypertension The urea nitrogen content of the blood was 100 mg per hundred cubic centimeters The spinal fluid was normal

The original stupor deepened, and death occurred, with the patient suffering from uremia, on September 8

Postmortem examination revealed periarteritis nodosa of the gastric arteries, small renal aneurysms, recanalization of the hepatic arterioles, hyalinized splenic arterioles, thickened pulmonary arterioles, adhesive pleurisy, bronchopneumonia, universal adhesive pericarditis, with calcification over the right ventricle, slight cardiac hypertrophy, an increased amount of connective tissue in the portal canals, and renal infarctions secondary to aneurysms ("the kidneys had marked atrophy with markedly decreased function of the parenchyma, more than would be expected from the gross appearance") No changes were noted in the central nervous system

*Summary*—An elderly man with epigastric pain and hypertension presented the clinical picture of glomerulonephritis and died in uremia Postmortem examination revealed periarteritis nodosa, with healed lesions involving principally the kidneys, stomach and liver

CASE 10—R S, a 7 year old Jewish boy, was admitted to the hospital on March 20, 1931 There was a history of whooping cough, measles, chickenpox, mumps and infrequent colds There had not been any suggestion of a rheumatic state Two months previously he had a mild attack of scarlet fever, with desquamation occurring within two weeks Fever, cervical adenitis and frequent epigastric cramps developed The following week, after the cessation of these symptoms, there was migratory pain in the ball of the right foot, right thumb and groin unassociated with any local signs, and finally pain developed in the scrotum

Dyspnea and pallor were noted for the first time two weeks before his admission to the hospital, when a diagnosis of rheumatic carditis was made though no other cardiovascular findings were then present

The child was of the so-called pituitary habitus and the size of a 14 year old child The heart was noted to be enlarged, the liver was palpable and the diagnosis of rheumatic fever was concurred in On roentgen examination the left ventricle was enlarged, and the lungs were diffusely mottled, the interpretation being mitral disease with pulmonary congestion

The hemoglobin content was 38 per cent The leukocyte count was 16,000 with 81 per cent polymorphonuclear cells All the laboratory tests gave normal results Fever persisted, the temperature occasionally reaching 105 F

Digitalis and salicylates were given. The general condition became worse, and death due to cardiac insufficiency occurred on April 10.

Postmortem examination revealed milium nodules related to the pulmonary arteries, a nodular coronary artery, a flabby myocardium, subacute verrucous rheumatic endocarditis of the mitral valve, a MacCallum lesion of the left auricle, thickened intrarenal arteries, granular deposits in the pleura, collapse of the lower lobe of the right lung, thickened pulmonary arteries and exudate-free bronchi.

Microscopically, acute periarteritis nodosa of the renal arterioles, parietal venous thrombi in the kidneys and lungs, recanalized arteritic lesions in the liver and heart and Aschoff bodies were noted.

*Summary*—A child of the Frohlich habitus had a mild attack of scarlet fever followed by epigastric cramps and articular pains. The subsequent clinical course and findings suggested acute rheumatic fever. Typical lesions of rheumatic fever and of periarteritis nodosa with some healing were present at necropsy.

CASE 11—S. M., a 10 year old American-born Italian boy, was admitted to the hospital on Oct. 2, 1923. Previously he had been well. For the past ten weeks he had had shooting pains in the extremities and trunk, generalized hyperesthesia and a temperature of 103 F.

Examination revealed pharyngitis, a palpable spleen, left ankle clonus and a pseudo Babinski sign. The diagnosis at that time was polyneuritis or polymyositis. The hemoglobin content was 85 per cent, and the leukocyte count, 14,000 with 80 per cent polymorphonuclears. The bleeding time and platelet count were normal. Several blood cultures were sterile.

Purpuric spots appeared soon on the back and in the pectoral region, and a positive tourniquet test was obtained. One swelling appeared along the outer aspect of the left humerus and several along the deltoid muscles and seemed to involve the periosteum.

Precordial pain developed, and hypertension increased, the pressure rising from 145 systolic and 112 diastolic to 176 systolic and 138 diastolic in several months. Finally there was clinical cardiac enlargement.

A biopsy specimen of muscle was taken, and dilated vessels with perivascular infiltration by polymorphonuclear leukocytes was noted. A flexor contracture developed. Gradually numbness in the left hand, ankle clonus, convulsions, nuchal rigidity, myoclonus and spontaneous hippus movements were noted. The fundi showed temporal exudate. At this time the spinal fluid contained 1,280 polymorphonuclear cells per cubic centimeter. There was no retention of urea nitrogen, and the urine was normal. The hematologic condition did not vary much throughout the entire course. The diagnosis then considered was a vascular lesion in the region of the midbrain or quadrigeminal plate, with meningitic and encephalitic phenomena. There was gradual improvement from the semiconsciousness into which the patient had lapsed to a state of deteriorated sensorium. Some ocular signs persisted. There was recurrent infection of the upper respiratory tract, and the left testicle became swollen. Death due to pneumonia occurred on March 27, 1924.

Postmortem examination revealed brown induration of the lungs, porphyrin-like kidneys with thickened interlobular arteries and some periarteritis nodosa, focal degeneration of the renal parenchyma and calcium deposits in the tubules, round cell infiltration of the periportal spaces, one periarteritis nodule of the adrenal gland, periarteritis nodosa of the muscles, pea-sized, sacculated aneurysms

of the coronary, gastric and gastric serosal arteries and miliary aneurysm formation in the pancreas, thickened hepatic and cystic arteries without aneurysms, and complete occlusion of one intrahepatic artery by thrombosis associated with periarteritis nodosa

*Summary*—An Italian boy had had generalized pain in the muscles, fever and pharyngitis for eight months. Persistent hypertension and encephalomeningitic symptoms developed. Extensively distributed periarteritis nodosa was present at necropsy.

CASE 12—J. S., a 51 year old Dutchman, was admitted to the hospital on Jan 16, 1931. The patient's first complaint was of parosmia six weeks previously. The right antrum was irrigated three weeks later, and two days after this procedure pain and inflammatory swelling of the right periorbital tissues appeared. Soon peripheral paralysis of the right facial nerve and complete nerve deafness on the right developed. No otitic discharge was present. The patient then complained of pain in the throat, dysphagia and tenderness of the anterior portion of the neck. Finally, on the day before his admission to the hospital, a red, painful swelling, about 5 cm in diameter, was noted in the region of the right malleolus.

Examination, in addition to the foregoing findings, revealed severe wasting, particularly of the muscles, emphysema and bronchitis. Tenderness over the sacrum and edema of the glottis were present. The right ear drum was thickened, gray and retracted. Taste was impaired on the right anterior portion of the tongue. Edema of the eyelids and chemosis of the left conjunctiva, episcleritis and iritis ensued. The fundi were normal.

The urine was normal. The Wassermann reaction of the blood and spinal fluid was negative. The leukocyte count was 18,400 with 85 per cent polymorphonuclear cells.

As the periorbital swelling subsided and the general condition appeared better, therapy for the condition of the sinuses was begun. The temperature, which had been normal, fluctuated regularly between 99 and 102 F. Cultures of pus removed from the right antrum on two occasions contained *Staphylococcus aureus* and *Staphylococcus albus*. The condition was considered to be due to chronic sepsis, with the focus probably in the sinuses. From time to time the patient complained of vagrant pain and tenderness in the right knee, the right epididymis, the sacrum and the left ear. Some impairment of hearing on the left and vesiculation of the posterior wall of the left canal were found. In three days this condition had progressed so that there were peripheral paralysis of the left facial nerve and complete deafness in the left ear, attributed to a lesion in the left geniculate ganglion.

The urine became grossly bloody about three months after the patient's admission to the hospital. There was no renal tenderness or enlargement. The possibility of periarteritis nodosa was suggested by the urologic consultant, Dr. Beer. The blood picture had changed, the leukocyte count was 12,000 with 38 per cent monocytes, suggesting monocytic leukemia in response to infection. The hemoglobin value had fallen, and several transfusions were given. There was no improvement, and the urine continued to be bloody. The patient became comatose, tremors of the upper extremities developed and death occurred on April 10.

Postmortem examination revealed periarteritis nodosa of the kidneys, testicles, heart and mesenteric arteries, brown, turbid, purulent material in the right antrum, chronic emphysema and chronic bronchitis, dilatation of the right ventricle and

parenchymatous degeneration of the myocardium, acute diffuse pancreatitis (normal ducts) and occasional hyalinization of the arterioles, splenic enlargement, with hemorrhagic foci, a few follicles, many large mononuclear cells, many colonies of cocci without polymorphonuclear reaction, foci of fibrosis and arteriolar hyalinization without arteritis, numerous aneurysms of the kidneys, with rupture of one into the left renal pelvis, compression of the renal parenchyma in the region of the aneurysms, occasional hyalinized glomeruli and arterioles, and moderate enlargement of the cerebral ventricles. A study of the brain was not completed. The bone marrow was normal.

*Summary*—Following maxillary sinusitis, there developed, in sequence, deafness, erythematous swellings on the extremities and vagrant tenderness, a Ramsay-Hunt syndrome of the left geniculate ganglion and hematuria. Because of the heterogeneity of the symptoms the diagnosis of periarteritis nodosa was suggested. The blood count was suggestive of monocytic leukemia. Lesions of periarteritis nodosa with rupture of an aneurysm into the renal pelvis were noted at necropsy.

CASE 13—J. G., a 50 year old Jew, was admitted to the hospital on Aug 18, 1928. He had had Pott's disease and pleurisy in childhood. He had been well until three weeks before admission to the hospital. At that time he suffered from acute antral sinusitis, and a nasal operation was performed. In the hospital the eyes were noted as being prominent and suffused, and a cavernous sinus thrombosis was suspected. The temperature was 104 F., the leukocyte count ranged about 19,000 with 90 per cent polymorphonuclear cells. The urine contained casts and red and white blood cells. A diagnosis of bacteremia with a primary focus in the sinuses and possibly associated nephritis was made. Pain developed in the right elbow and left shoulder, and there was also bloody expectoration.

Ulcerations appeared on the tongue and buccal mucosa. Hemorrhagic cutaneous lesions, considered as a toxic manifestation secondary to miliary tuberculosis, appeared. However, the lingual lesions disappeared more rapidly than could be accounted for on the basis of tuberculosis. A rash, consisting of purpuric lesions, appeared. The lesions changed to fawn-colored maculopapules from several millimeters to several centimeters in diameter, these faded on pressure. They were of generalized distribution but most numerous on the neck and trunk. They were considered as erythema multiforme in the course of tuberculosis.

The sputum had shown tubercle bacilli on two occasions. A roentgenogram of the chest made a week after the patient's admission to the hospital showed no evidence of tuberculosis, but in two weeks small nodular infiltrations were noted in the apex of the right lung.

Cystoscopy was performed because of the urinary findings and disclosed obstruction of the left ureter.

Fever was present throughout. Blood cultures were sterile. The pressure and the urea nitrogen content of the blood were normal.

Postmortem examination revealed kyphoscoliosis, hemorrhagic spots on the dorsa of the hands and forearms, thighs, knees and abdomen, perioral herpes, necrotizing tracheobronchitis and calcification of the tracheobronchial lymph nodes, pulmonary nodules, small hemorrhages, infarcts and perivascular thickening of the small vessels of the kidneys, a calculus in the left kidney, and periarteritis nodosa of the ileum.

Microscopically there were endarteritis of the coronary arteries, peribronchial infiltration, periarteritis nodosa of the pulmonary arterioles, focal necrosis and periportal fibrosis of the liver with perivascular infiltration and fibrinoid changes in the intima, and periarterial infiltration of the mesenteric, gastric and small cutaneous arteries

*Staph aureus* and *Staph albus* but no tubercle bacilli were cultivated from material from the lung

*Summary*—In a man of 50 with sinusitis, for which an operation had been performed, articular pains, bloody expectoration, oral ulcerations, cutaneous hemorrhagic lesions and nephritis accompanied with fever developed. These were considered a reactivation and dissemination of tuberculosis. Postmortem examination revealed old tuberculous pleurisy and periarteritis nodosa

CASE 14—S. A., a 72 year old Jew, was admitted to the hospital on Jan 25, 1931. Previously he had had typhoid (sixty years before), arthritis of the right shoulder (fifteen years before) and, in the past two years, dyspnea on exertion, intermittent claudication and slight nocturia. Six months before his admission to the hospital he suffered a sudden sticking pain in the left lower portion of the chest which radiated into the abdomen and was aggravated by respiration. It was followed by a duller pain, which lasted for a week and was superseded by a sharp, colicky pain in the epigastrium which radiated into the right upper quadrant of the abdomen and into the back. The stools became light yellow and the urine dark. There was nonpruritic jaundice. The pain continued intermittently for about a month, and the jaundice and associated findings improved. There was a loss of 15 pounds (7 Kg) in this period.

In addition to slight icterus, the initial physical examination showed disseminated purpuric lesions on the skin, generalized cardiac enlargement, extrasystoles, ascites, slight enlargement of the liver, and slight pitting edema over both ankles. Examination of the fundi revealed the arteries to be somewhat thin and irregular, with indentation of the veins.

The hemoglobin value was 90 per cent, and the leukocyte count, 10,700, with 90 per cent polymorphonuclears. The icteric index was 55. The blood pressure was 145 systolic and 80 diastolic. The bleeding, clotting and clot retraction time were normal. The stools contained no blood, urobilin was present. Abdominal puncture yielded a serohemorrhagic fluid, with 70 per cent polymorphonuclear leukocytes. The Wassermann test of the blood was negative. The blood sugar content was 115 mg per hundred cubic centimeters. The urea nitrogen content at the time of the patient's admission to the hospital was 81 mg, and it rose finally to 166 mg. The urine contained a moderate amount of albumin, bile and urobilin but no cells or casts. The electrocardiogram showed preponderance of the left ventricle.

The icterus receded, but the patient's general condition became worse. The temperature varied from subfebrile to subnormal. He became drowsy, and vomiting, some muscular twitchings and tenderness high in the abdomen were noted. He died on January 30. He was considered to have a malignant growth with metastases to the liver.

Postmortem examination revealed slight icterus, disseminated, irregularly confluent bluish red lesions in the groins and axillae, serous peritoneal fluid, obliterating adhesions of the right pleural cavity, fibrinous granules of pericardium at the base of the heart, fresh adhesions over the great vessels, fibrinous exudate over the auricles, moderate brown induration of the lungs,

gangrene of the right auricle, subendocardial hemorrhage of the left papillary muscle, thickened, occasionally thrombotic arterioles of the liver, one periarteritic nodule of the gallbladder, one patch of necrosis in the pancreas, petechial and linear hemorrhages and hemorrhagic cysts of the kidneys, esophagitis, with lesions resembling those of the skin, and diffuse hemorrhage of the gastric, jejunal and ileal mucosa

Microscopically there were noted hyalinization of many glomeruli, with some anemic and some congested glomeruli and some partially necrotic glomeruli without inflammatory reaction, hyalinization of the arterioles, intimal thickening of the interlobular arteries and some focal necrotizing arteritis with adventitial infiltration, acute necrosis and hemorrhage of the entire right auricle, fibrosing arteritic lesions of a definite inflammatory type, with narrowing of the lumen of the coronary arteries, hemorrhages with arteritis of the gastro-intestinal tract, acute necrotizing arteritic lesions with polymorphonuclear leukocytic infiltration of the liver, acute inflammation of the periportal spaces and polymorphonuclear leukocytes and bile thrombi within the small bile ducts, typical acute arteritic lesions and congested capillaries involving the gallbladder, healed arteritis of the pancreas, and small foci of necrosis with hemorrhagic and acute arteritis of the adrenal glands

*Summary*—In an aged man with symptoms of moderate cardiac insufficiency pain suddenly developed in the epigastrium and in the lower left portion of the chest, followed by moderate icterus and was attributed to a metastatic malignant condition of the liver. He died in uremia. Necropsy revealed polyserositis, periarteritis nodosa, gangrene of the right auricle and arteriolitis of the kidneys

CASE 15—J. B., a 30 year old British West Indies Negress, was admitted to the hospital on Aug. 6, 1933. This patient had spent most of her life in the United States. She had had a febrile illness associated with puffiness of the eyelids and two attacks of rheumatic fever in girlhood. She had since been well except for mild cardiovascular symptoms and constipation until one month before her admission to the hospital. There was a family history of hypertension.

The presenting symptoms developed rapidly: violent headaches, blurring of vision, nocturia, intermittent hematuria, dysuria, precordial pain, palpitation, dyspnea, orthopnea, nausea, vomiting and abdominal pain. She had pain in the right anterior portion of the chest and cough productive of mucus and occasional flecks of blood for three days. She became increasingly drowsy. The eyelids were puffy.

At the time of her admission to the hospital the patient was twitching, and her breath was urinous. The fundi showed papillitis, destruction of the disk markings, linear hemorrhages, old retinal exudates and narrow, irregular arteries.

The heart was generally enlarged, and a long, blowing diastolic murmur was heard, best at the apex, where there also was a gallop rhythm. The pulmonic and aortic second sounds were duplicated.

There was bilateral costovertebral tenderness due to shock, and slight tenderness was noted in both lower quadrants of the abdomen.

The blood pressure was 206 systolic and 146 diastolic, the hemoglobin content 45 per cent and the leukocyte count 9,500 with 80 per cent polymorphonuclear cells. The urea nitrogen content was 115 mg. per hundred cubic centimeters of blood. The urine was of low specific gravity and contained much albumin and many red and white blood cells.

The patient was considered to have chronic cardiovascular disease of rheumatic etiology, with uremia on the basis of either chronic glomerulonephritis or malignant sclerosis

Shortly after the patient's admission to the hospital pulmonary edema developed. An electrocardiogram at this time showed an inverted T wave and marked left ventricular preponderance. Disease of the coronary arteries was considered to be present. There was no response to therapy.

Postmortem examination revealed malignant nephrosclerosis, generalized arteriosclerosis, hypertrophy of both ventricles, partial obliteration of the coronary arteries, hemorrhagic gastritis, ileitis with ulcerations, cystitis, vascular lesions of the wall of the gallbladder and periarteritis nodosa of the stomach, intestines, gallbladder and adrenal glands.

*Summary*—A Negress, with a previous history of rheumatic fever, showed symptoms of mild cardiac insufficiency about one month before her admission to the hospital and finally hypertension and uremia. Malignant nephrosclerosis, periarteritis nodosa and hemorrhagic lesions of the gastro-intestinal tract were present at necropsy.

CASE 16—S. W., a 37 year old Jewish baker, was admitted to the hospital on June 26, 1933. He had been asthmatic for two years and had been found to be sensitive to feathers, wheat, flour and barley. Operations on the nose and sinuses and tonsillectomy had been followed by slight improvement in the symptoms. No hay fever or urticaria had been present. There was no history suggestive of any other chronic illness. He had lost about 50 pounds (22 Kg.).

About seven weeks before his admission to the hospital a pustular, occasionally sanguineous rash appeared over his face and was attributed to some unidentified medication. Sharp, continuous pains and weakness and stiffness of the right hand then developed. About five weeks later watery diarrhea, tenesmus and periumbilical cramps set in. The stool on occasion was purulent and frankly bloody.

At the initial examination the patient seemed cachectic, acutely ill and in asthmatic dyspnea. White-centered petechiae were present on the conjunctiva, the soft palate and the shoulders and arms. Multiple erythematous macules were distributed over the face. A polypoid mass was palpable in the rectum. The extremities were wasted. The right hand was pale and swollen, and there was glove-like hypesthesia. Right ankle clonus was present. No other positive neurologic signs were elicited. There was tenderness over the sacrum, the lower cervical portion of the spine, the sternum and the left ninth and tenth ribs. The fundi were normal.

On sigmoidoscopy an atypical ulcerating lesion was observed, which on biopsy was considered to be of a nonspecific inflammatory type.

The diagnosis, also suggested by roentgen examination, was an ulcerative lesion of the rectum, either nonspecific or due to emebic colitis associated with purpuric manifestations and peripheral neuritis due to avitaminosis or nutritional deficiency.

The blood picture, temperature and neuritis remained unchanged for about two months. A confluent petechial eruption appeared over the right iliac crest. It was considered a toxicoderma of an erythema multiforme type. Diarrhea persisted, with the occasional appearance of occult blood in the stool. Gastro-intestinal roentgenograms became negative. Roentgenograms of the chest showed coarse infiltrations in the lower lobe of the left lung, suggesting resolving pneumonia.



Edema of the ankles and eyelids appeared, that involving the eyelids being strikingly localized and nonpitting

A period of remission followed in which the abdominal pain, diarrhea, fever and leukocytosis disappeared. A barium sulfate enema revealed no abnormality. There was no significant change in the patient's general condition after a transfusion was given.

On August 14, in this period of apparent improvement, there suddenly occurred severe abdominal pain, with rigidity, tenderness and obliteration of the hepatic dulness. Bloody mucoid sputum was expectorated. The diagnosis was generalized peritonitis secondary to a perforated viscus. Death occurred in several hours.

Postmortem examination revealed an erythematous maculopapular eruption on the forehead and cheeks, edema of the ankles and eyelids, generalized cardiac hypertrophy and dilatation, diffuse myocardial fibrosis and focal areas of subacute myomalacia cordis, parietal thrombosis of the right and left ventricles, thrombosis of the left auricular appendage, thrombosis of the small branches of the pulmonary artery of the lower lobes with multiple infarctions, serosanguineous fibrinous pleurisy on the left and hydrothorax on the right, a chronic callous peptic ulcer, with perforation and fibrinopurulent peritonitis, multiple gastric erosions and a small peptic (unperforated) ulcer, multiple anemic infarctions and scarring of the kidneys, and periarteritis nodosa of the heart, lungs, kidney, mesentery, gallbladder, testes and stomach.

*Summary*—A man who had had asthma and proved sensitivity, which appeared for the first time two years before his admission to the hospital, became ill with peripheral neuritis and ulcerative colitis. During a remission a perforated gastric ulcer suddenly developed, and death followed. At necropsy periarteritis nodosa, a perforated gastric ulcer, peritonitis and multiple gastric erosions were present.

CASE 17—M. K., a 19 year old woman, was admitted to the hospital on June 4, 1928. She had had frequent attacks of tonsillitis in childhood. Six months before her admission to the hospital she had articular pains, followed by abdominal pain and vomiting for five weeks. Appendicitis and intestinal obstruction were diagnosed, and an appendectomy was performed. Subacute catarrhal appendicitis was present. There was a remission of the symptoms for four months. Symptoms of cardiac insufficiency and also albuminuria, pleural effusion and fever then developed. When admitted to the hospital the patient was in collapse, the heart sounds were distant and a pericardial friction rub was present. The lungs showed signs of fluid and of superjacent compression. The blood pressure was 98 systolic and 70 diastolic, the hemoglobin value 52 per cent and the leukocyte count 10,200. The urine contained albumin (four plus), casts and white blood cells. The urea nitrogen content was 41 mg per hundred cubic centimeters of blood. The temperature ranged between 98 and 104 F, and the pulse rate was about 120.

Signs of recurrent pleurisy appeared, though no fluid was obtained on aspiration. The face became puffy and the throat red, and pains were noted in the right costovertebral angle and in the large joints. Bilateral ulnar neuritis and an urticarial lesion of the hypothenar process appeared. In the course of the next four months the blood pressure rose gradually to 150 systolic and 116 diastolic, the urea nitrogen content was 77 mg per hundred cubic centimeters of blood, the urine contained red blood cells and the hemoglobin content fell to 35 per cent, with only a transient response to a transfusion of blood.

Abdominal pain which was not controlled by codeine again appeared. On October 8 death occurred with the patient in uremia. Blood cultures had been sterile. The clinical diagnosis was the indeterminate type of bacterial endocarditis and acute arteritis. (The changing clinical and roentgenographic pulmonary findings are described in the text.)

Postmortem examination revealed generalized, irregular, fine, discrete, purple hemorrhages the size of a pinhead involving the skin and the aponeurotic layer of the scalp, chronic fibrinous pleurisy and pleurisy with effusion, bullous edema of the visceral and diaphragmatic pleura, wedge-shaped hemorrhages in the lungs, no changes in the pulmonary vessels, adhesive pericarditis with sacculated spaces between the apposing surfaces, edema of the surface and base of the heart associated with fresh hemorrhages, focal myocarditis, subacute verrucous endocarditis of the mitral and aortic valves, arteritis of the small arterioles, peritoneal effusion, fatty degeneration of the liver, with a thickened capsule, circumscribed areas of hemorrhage and of superficial ulceration of the mucosa of the stomach near the lesser curvature and on the posterior surface, anemic infarcts of the spleen, necrosis of the pancreas, thickening and edema of the capsule of the left kidney, numerous flame-shaped hemorrhages of the renal parenchyma, one thrombosed vein at the pyelovenous angle of a calyx, gelatinous edematous exudate beneath the pia-arachnoid, and moderate congestion of the cerebral vessels.

Vegetation from the aortic and mitral valves contained gram-positive cocci overgrown by colon bacilli.

Microscopically there were panarteritis and focal periarteritis of the stomach and mesentery, several areas of hemorrhage and necrosis in the medulla, focal proliferation of the nuclei of some glomeruli, slight interstitial fibrosis, and foci of necrotizing arteritis with slight periarteritis, hyaline changes in the vessels, perivascular infiltration with glia cells and fibrosis and occasional pigment-laden gitter cells in the perivascular spaces.

*Summary*—A patient with recurrent tonsillitis was ill for about a year with articular pains, abdominal pain (for which appendectomy was performed), pleural and pericardial effusions, renal insufficiency, progressive anemia and hypertension. The clinical diagnosis was the indeterminate type of bacterial endocarditis and acute arteritis. This was confirmed at postmortem examination, the arteries being typical of "periarteritis nodosa," involving particularly the heart, kidneys and stomach. A meningeal exudate was present. The endocardial vegetations contained gram-positive cocci.

#### PRODROMAL ILLNESS AND MODE OF ONSET

Gruber's analysis indicated that this syndrome is superimposed on an infectious or septic state. Other recent observers have reported as follows

- Dietrich Erysipelas of the forearm of two months' duration
- Gray Posttraumatic cellulitis of the left thigh with inguinal lymphadenopathy
- Hampel and Conta Postdiphtheritic cardiac disease complicated by pulmonary periarteritis nodosa
- Lindberg An infected wound of the foot followed by articular pain and fever lasting for one month and merging with localized pains in the bones
- Klotz (second case) Acute rheumatic fever of three years' duration, grip of two months' duration
- Herrman Myalgias
- Helpert and Trubek Gonorrhea
- Moolten Meningococcal meningitis

Seven of our series of 17 patients suffered from known prodromal illness of a banal type, such as acute tonsillitis or acute sinusitis, which merged with symptoms attributable to periarteritis nodosa without an intervening period of good health. Scarlet fever of atypical form occurred in 2 other patients in the two months preceding the appearance of arteritic symptoms. The prodromal illness generally seemed a specific disease entity.

TABLE 1—*Data on Seventeen Cases of Periarteritis Nodosa*

Case	Remote History	Prodromal Illness	Duration of Symptoms Before Periarteritis Nodosa	Symptoms of Onset of Periarteritis Nodosa
1	Recurrent acute tonsillitis, gonorrhea	Acute tonsillitis	1 month	Abdominal pain, pain in joints
5		Acute tonsillitis, pain in joints	3 weeks	Abdominal pain
6	Typhus, recurrent peritonsillar abscesses	Acute tonsillitis	Coincident	Pain in legs, testicle, abdomen (renal type)
12		Acute sinusitis	6 weeks	Peripheral facial neuritis
13	Pott's disease, pleurisy	Acute sinusitis	3 weeks	Pain in joints, lesions of mucous membrane
17	Recurrent acute tonsillitis	Pain in joints	Several weeks	Abdominal pain
8		Atypical scarlet fever	7 weeks	Abdominal pain
		Urticaria, pain in joints	1 month	
10		Mild scarlet fever, pain in small joints	2 months	Cardiac insufficiency
11		Pain in joints	10 weeks	Precordial pain
16		Asthma, sensitivity to feathers, etc	2 years	Peripheral neuritis, cutaneous lesions
3	Recurrent pain in joints			Pain in right lower quadrant of abdomen
15	Rheumatic fever (twice), acute nephritis			Abdominal pain, renal and cardiac insufficiency
7	Pleural pain on the right			Abdominal pain, renal and cardiac insufficiency
2, 4				Abdominal pain
9				Abdominal pain, pain in leg
14	Typhoid, arthritis			Pain in abdomen and chest

One patient (case 16) had a two year period of asthma and showed manifest sensitivity to feathers, wheat flour and barley. This is the only ascertained instance in which an undisputedly allergic state was intimately associated with the syndrome of periarteritis nodosa. Lamb's first patient had a two year history of asthma and of associated urticaria. However, specific sensitivity was not demonstrated.

In 2 other cases the remote history revealed illnesses which might have been contributory to periarteritis nodosa, the third patient had fleeting articular pains, and the fifteenth patient had two attacks of rheumatic fever and one of acute nephritis. These factors were not, strictly speaking, prodromal.

After the initial illness had persisted for a variable period, generally for about two months, symptoms of a different type appeared, which

in retrospect, were those of periarteritis nodosa. In 8 cases there was no known prodromal illness. The mode of onset varied as follows. Eleven patients had abdominal pain. About 5 of these had a closely associated history of articular pain, and 2 others had cardiac and nephritic symptoms. Two had cardiac symptoms and articular pains, and 2 had peripheral neuritis, in 1 of these there were also cutaneous

TABLE 2—*Cardiac Lesions in Periarteritis Nodosa*

Case	Endocarditis	Myocarditis	Pericarditis	Disease of Coronary Arteries	Other Lesions
1	Verrucae (mitral)	Aschoff bodies	+	Nodules	Enlargement of heart
4		Recent fibrosis and necrosis		Intimal proliferation	Enlargement of heart
5				Aneurysms	Enlargement of heart
6				Aneurysms	Hemorrhage in the pericardial sac
7			+	Microscopic periarteritis nodosa, parietal thrombus of coronary artery	Enlargement of heart
8	Acute verrucae (mitral)	Aschoff bodies	+	Microscopic periarteritis nodosa	Enlargement of heart
9			Adhesive pericarditis, patch of calcification		
10	Subacute verrucous rheumatic endocarditis (mitral), MacCallum lesion of left auricle	Aschoff bodies, myocarditis		Nodule	Enlargement of heart
11				Aneurysm	
12		Parenchymatous degeneration		Nodules	Enlargement of heart
13				Endarteritis	
14			Granular pericarditis, fresh adhesions	Microscopic periarteritis nodosa	Necrosis of right auricle
15		Aschoff bodies			
16		Diffuse fibrosis and myomalacia		Nodules	Enlargement of heart, parietal thrombus of ventricles and left auricle
17	Subacute endocarditis, verrucae (mitral and aortic), large vegetation (mitral and aortic)	Focal myocarditis	Adhesive pericarditis, bullous edema, hemorrhages	Microscopic periarteritis nodosa	Enlargement of heart

lesions and articular pains. Abdominal pain, not adequately explained by involvement of a single organ, was the most usual presenting symptom. One suggestive association was the combination of abdominal pain with apparently irrelevant symptoms, for instance, of arthritis, nephritis or cardiac insufficiency.

The syndrome, for some unknown reason, involves males more frequently than females, in Gruber's series 80 per cent of the patients were male, while the proportion in our much smaller series was 12 males to 5 females. The age range is from infancy to old age. The occur-

rence of periarteritis nodosa in childhood has been the subject of study by Rothstein and Welt<sup>16</sup>

The known duration of the disease is measured in weeks and occasionally in months. The briefest history is recorded by Thunnes<sup>17</sup> in an infant who was ill for less than a day with acute pharyngitis and apparent abdominal pain before death occurred.

#### CARDIAC INVOLVEMENT

Varied cardiac lesions were present in all the cases in which a post-mortem examination was made. The typical lesions of periarteritis nodosa involved the coronary arteries in 11 of the 15 cases. In 1 of these the condition was complicated by hemorrhage into the pericardial sac secondary to rupture of an aneurysm, in another case necrosis of an auricle occurred owing to the arterial lesion. According to the survey made by Powell and Pritchard,<sup>18</sup> 77 of 150 patients had cardiac lesions directly due to periarteritis nodosa.

Healed periarteritis nodosa, according to Jager,<sup>19</sup> may terminate in a lesion closely resembling that of arteriosclerosis, particularly in relatively young persons.

Four of our patients showed Aschoff bodies and verrucae of the mitral valve, and 3 of these patients with rheumatic heart disease showed gross periarteritis nodosa of the coronary arteries. Six patients had pericarditis. The third patient, who had a nonfatal, apparently arrested condition, showed clinical signs of mitral stenosis. The relation of the rheumatic state to periarteritis nodosa will be considered in a later section.

Inverted T waves were found in 4 cases of periarteritis nodosa in which repeated electrocardiographic tracings were taken.<sup>20</sup>

The clinical diagnosis of "indeterminate types of verrucous endocarditis and acute arteritis" in case 17 is noteworthy in that it suggests an identity between the condition in some cases of this group and periarteritis nodosa.<sup>21</sup>

16 Rothstein, J. L., and Welt, S. Periarteritis Nodosa in Infancy and in Childhood, *Am J Dis Child* **45** 1277 (June) 1933.

17 Thunnes, cited by Rothstein and Welt<sup>16</sup>.

18 Powell, R. E., and Pritchard, J. E. Report of a Case of Periarteritis Nodosa Involving One Kidney, *Brit J Urol* **4** 317 (Dec.) 1932.

19 Jager, E. Zur histologischen Ausheilung der Periarteritis nodosa und deren Beziehung zur juvenilen Atherosclerose, *Virchows Arch f path Anat* **288** 833, 1933.

20 Master, A. M., and Jaffe, H. Electrocardiographic Evidence of Cardiac Involvement in Acute Diseases, *Proc Soc Exper Biol & Med* **31** 931 (May) 1934.

21 Gross, L. The Heart in Atypical Verrucous Endocarditis, in *Contribution to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues*, New York, International Press, 1932, vol. 2, p. 527.

Hypertension was present in 5 patients when they were admitted to the hospital (cases 4, 5, 7, 9 and 15) and was observed in its rapid development during hospitalization in 4 other cases (cases 1, 6, 11 and 17). All but 1 of these patients showed associated abnormal urinary findings, and all of them had renal lesions.

TABLE 3—*Pulmonary Lesions in Periarteritis Nodosa*

Case	Pulmonary Symptoms	Time	Roentgen Findings	Necropsy Observations of Lungs
Lesions Directly Dependent on Periarteritic Nodules of Pulmonary Arteries				
1	Slight cough		Lobular pneumonia of lower lobe of right lung	Submiliary nodules, small thrombosed vessels, no infarctions
7	Pleural pain, questionable basal bronchopneumonia of left lung			Necrotic infarctions with pleural fibrin reaction dependent on blood vessel with fibrosed recanalized thrombus
10			Diffusely mottled lungs	Miliary nodules related to pulmonary arteries
13	Bloody expectoration, tuberculous ?		Small nodular infiltration of apex of right lung	Necrotizing tracheobronchitis, peribronchial infiltration, nodules, periarteritis nodosa with occlusive thrombi, no caseation
16	Asthma		Coarse infiltrations in lower lobe of left lung suggesting resolving pneumonia	Fibrinous pleurisy on left, hydrothorax on right, periarteritis of lungs with associated infarctions
17	Pleural pain	Early June	On admission, a small pleural effusion at extreme base of left lung, slight general enlargement of heart, probably due to mitral lesion	Mottled, circumscribed hemorrhages, somewhat dilated pulmonary vessels, adhesive pleurisy and effusion
		Middle of June	In 2 weeks, increase in effusion in chest	
		July	In 2 weeks, nearly complete resolution of pneumonia, small effusion at base of left lung	
		August	In 1 month, more effusion of left lung, increase on right side, infiltrations extending out from hilus in region of middle lobe	
		End of August	In 2 weeks, diminution of pleural effusion on left, some evidence of pleural thickening in this region	
Lesions Associated with Periarteritis Nodosa of Pulmonary Arteries				
16	Terminal bronchopneumonia			Patchy consolidation
8	Bilateral bronchopneumonia, pleural friction rub on left			Pulmonary congestion
9	Bronchopneumonia			
11	Bronchopneumonia			Indurated, brownish lungs
14	Pleural pain on left			Indurated lungs

A systolic murmur was audible in 2 of our cases (2 and 8) and a pericardial friction rub in 4 of our cases (1, 7, 9 and 17) in which pericarditis was present at necropsy. Precordial pain occurred in 3 (cases 1, 11 and 15) and dyspnea in 2 (cases 6 and 10). No case of arrhythmia was recorded.

Incidentally, it may be of diagnostic significance to note that the patients who had rheumatic fever clinically did not respond to treatment with salicylates.

## PULMONARY LESIONS

The opinion is current that the lungs are generally exempt from periarteritis nodosa. The first instance of lesions of the pulmonary artery was reported in 1905 by Monckeberg.<sup>22</sup> Only 4 of Gruber's patients had such involvement. Sternberg reported a fatality due to pulmonary hemorrhage.

Herrman<sup>23</sup> cited the case of a patient with asthma who showed extreme involvement of the small branches of the pulmonary arteries and another with a "cigaret cough" who showed the typical clinical course of periarteritis nodosa, frequent roentgenograms being made. Since his was the first published case in which a roentgenographic study was made, the details will be summarized. Initially the films and the physical signs were normal. In six weeks, while the physical signs remained normal, the roentgenograms showed "diffuse perivascular infiltration spreading out uniformly and equally from both hilar regions." The interpretation was that small infarctions or possibly bronchopneumonia was present. A week later there was "increased confluence indicating further exudation with suggestion of beginning solution or cavitation." In several months there were questionable infarction and effusion. At postmortem examination, in addition to periarteritis nodosa, there were chronic pleuritis and multiple pulmonary infarctions dependent on thrombotic arteries with periarteritis nodosa.

Conta's<sup>24</sup> case was that of a 16 year old boy who had shown post-diphtheritic cardiac symptoms since the age of 4 years. He died of typical heart failure. Roentgenograms showed shadows, ranging in size from that of a lentil to that of a cherry, particularly near the hilus of the right lung, and small pneumonic infiltrations. At necropsy mitral stenosis, adhesions of the right pleura and periarteritis of the pulmonary artery were noted. The heart, liver and kidneys were involved.

Matillon<sup>25</sup> reported a case of periarteritis nodosa in a woman aged 73 with the clinical course of bronchopneumonia.

In Ophuls'<sup>26</sup> patient, who had asthmatic breathing, there were extensive involvement of the small branches of the pulmonary arteries and

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22 Monckeberg, cited by Ceelen, W. Die Kreislaufstorungen der Lunge, in Henke, F, and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1931, vol 3, pt 3, p 33.

23 Herrman, W. Pulmonary Changes in Case of Periarteritis Nodosa, Am J Roentgenol **29** 607 (May) 1933.

24 von Conta. Periarteritis nodosa der Lungengefasse und Lungenrontgenbild, Fortschr a d Geb d Rontgenstrahlen **47** 506, 1933.

25 Matillon, B. La periarterite noueuse, These de Paris, no 460, 1928.

26 Ophuls, W. Periarteritis Acuta Nodosa, Arch Int Med **32** 870 (Dec) 1923.

also diffuse infiltration of the bronchial tubes and the pulmonary parenchyma with eosinophils

The foregoing is a fairly comprehensive summary of the reported cases of pulmonary involvement in periarteritis nodosa. Five patients in our series had pulmonary lesions immediately dependent on the typical vascular changes of periarteritis nodosa. In 6 the pulmonary lesions were not of an arteritic type. It is apparent that the exemption of pulmonary arteries and tissue has been exaggerated.

In addition, examination of the accompanying table suggests the following conclusions: 1. Pleural pain is an expression either of primary pleurisy or of pleurisy secondary to extensive pulmonary infarction. 2. The roentgen findings may be suggestive of bronchopneumonia or of a small effusion. 3. The roentgen and postmortem pulmonary observations are more extensive than the clinical findings suggest. 4. The symptoms are variable and though obscure clinically may ultimately be satisfactorily correlated with the type of pulmonary lesion.

#### RENAL LESIONS

That renal impairment is the most usual accompaniment of periarteritis nodosa has been frequently demonstrated. Arkin<sup>27</sup> listed the incidence as high as 80 per cent, 83 of Gruber's 115 patients had renal lesions. All the patients in our series who were completely examined, including necropsy, had renal involvement. Those in whom no renal disorder was evident are still alive and asymptomatic.

Gruber's analysis showed the following lesions:

	Cases
Renal infarctions	35
Glomerulonephritis	21
Interstitial inflammation	2
Degenerative changes in kidneys	5
	<hr/> 63

In our series of 17 cases the involvement was as follows:

	Total Number of Cases	Urea Nitrogen Retention, Hypertension and Pathologic Urinary Condition, Number of Cases
Renal infarctions and aneurysms	8	4
Acute periarteritis nodosa	2	1
Glomerulonephritis	3	3
Arteriosclerosis	1	1
Malignant sclerosis	2	2
Focal degeneration	1	1
	<hr/> 17	

\* In case 17 there were renal infarctions, proliferation of the nuclei of the glomeruli and necrotic arterioles, and the case is entered under the three headings.

Gruber classified the renal changes as passive and active. In the former group are lesions directly dependent on the vascular involvement—thus, infarctions, renal and perirenal hematomas and atrophied

<sup>27</sup> Arkin, A. A Clinical and Pathological Study of Periarteritis Nodosa, *Am J Path* 6:401, 1930.



tubules The active changes are those which presumably were initiated by the factors underlying the periarteritis nodosa and which might be present without accompanying local periarteritis lesions This is particularly applicable to cases of glomerulonephritis and also to a minor group of cases of interstitial paravascular focal nephritis (Ophuls and Otani<sup>28</sup>)

As was pointed out by Gruber, there is no consistent correlation between the urea nitrogen retention, the hypertension and the abnormal urinary findings and any specific type of renal lesion These clinical findings may depend on the extent of renal impairment and also on the extent of vascular damage of the entire body The seventeenth patient had several types of renal lesions, as indicated in the table, and this multiple reaction actually may occur more often than has been supposed

The majority of our patients showed the anticipated lesions of acute periarteritis, of gross aneurysms and of infarcts secondary to these It remains to be considered whether the lesions of glomerulonephritis, of malignant sclerosis and of arteriosclerosis of the kidney, which occurred in the other cases, were merely a casual correlation of one vascular disease with another rare vascular disease or whether these too are to be grouped with periarteritis nodosa as mutants in vascular hyperergy This topic will be discussed in a subsequent section

Occasionally the renal lesions have required surgical intervention Retroperitoneal hemorrhage has occurred, and massive hemorrhage from the cortex has been reported by Harris and Friedrichs Powell and Pritchard<sup>18</sup> published a report of nephrectomy performed for hematuria and suspected renal calculus The diagnosis was made by examination of the kidney Myositis developed postoperatively However, the patient was clinically well for at least a year

Our sixth patient had gross hematuria at the onset, for which laparotomy was performed, thereby establishing the diagnosis The thirteenth patient died of renal hemorrhage

#### LESIONS OF THE DIGESTIVE ORGANS

It has been frequently stated that the symptoms of periarteritis nodosa mimic acute surgical conditions The diagnostic dilemma is even more difficult, since grave surgical complications are often present, as illustrated in the following 7 cases in our series

Case	
4	Ulceration of the jejunum with hemorrhage
5	Ulcer of the small intestine to which the greater omentum was adherent by fibrinopurulent exudate
6	Perirenal hematoma, four gastric ulcers
7	Ulceration of the small intestine and fecal peritonitis
14	Hemorrhagic ulceration of the gastro intestinal tract
15	Hemorrhagic gastritis and ulcerative ileitis
16	Gastric erosions and ulcers (one perforation)

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28 Otani, cited by Gruber<sup>9</sup>

This incidence of gastro-intestinal ulcer in 15 cases at necropsy is striking. Reported references to this condition are few. As early as 1904 Versé<sup>29</sup> reported a case in which there was rupture of ileal and jejunal ulcers. Gruber's<sup>30</sup> nineteenth patient had a ruptured jejunum. Recently in a child a perforated gastric ulcer and simple ulcers of the pylorus and duodenum were present, all on the basis of periarteritis nodosa. Most bizarre in this connection was case 16, in which there were constantly changing gastro-intestinal symptoms, carefully observed both clinically and roentgenographically under the diagnosis of ulcerative colitis. The one gastric ulcer which had perforated was of the typical callous peptic variety and was definitely associated with the local lesions of periarteritis nodosa.

Periarteritis nodosa undoubtedly is an occasional cause of hemorrhagic pancreatitis, for instance in cases 6, 7 and 15. In case 6 the diagnosis of periarteritis nodosa was established during exploratory laparotomy, at the same time the head of the pancreas was observed to be enlarged, and an area of fat necrosis was present in the omentum. At necropsy several months later the pancreatic vessels were obliterated by thrombi.

In Klotz' second case, that of a 53 year old man, apparently with acute rheumatic fever, death occurred suddenly, and hemoperitoneum involving the gastrocolic omentum and pancreas was present. Three of the patients studied by Gruber had pancreatic lesions—hemorrhage, periarteritic nodules and infarcts. In Lamb's second patient infarcts of the pancreas were present.

Three cases of periarteritis nodosa with involvement of the appendix were observed in this series, and the involvement varied in clinical intensity from very mild to severe. It seems likely that clinically and even pathologically mild involvement, as in cases 2 and 3 (unequivocal (periarteritis nodosa), may occur and escape notice. For instance, Kengyel<sup>31</sup> reported the case of an elderly woman with chronic polyarthritis who had a sudden attack of pain in the right lower quadrant of the abdomen. At laparotomy the ileum was incarcerated. At necropsy there was a healed arteritic process in the intestine, death was attributed to renal insufficiency.

In another case, not included in our series, the lesions of the appendix were slight in comparison to the usual, more foudroyant expression of the syndrome and were of the type called necrotizing arteriolitis,

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29 Versé. Periarteritis nodosa und Arteritis syphilitica cerebialis, Beitr z path Anat u z allg Path **40** 409, 1907.

30 Gruber, G. Ueber die Pathologie der Periarteritis nodosa, Zentralbl f Herz-u Gefasskr **9** 45 (April) 1917.

31 Kengyel. Centralbl f allg Path u path Anat **53**:137 (Dec) 1930.

described by Plaut,<sup>32</sup> in appendixes removed in the course of operations for other purposes and in the fallopian tubes. These lacked the gross aneurysms and the extensive anatomic distribution of periarteritis nodosa, an exact identity has not been established. However, the histologic resemblance is important, because it suggests that there may be an attenuated form of periarteritis nodosa.

Hepatic involvement was noted in 70 of a series of 150 recorded cases. The symptoms were icterus and, less frequently, pain in the right upper quadrant of the abdomen. Jaundice occurred in both of Klotz' cases, pain was present in the right upper quadrant of the abdomen in the first case, in which there were extensive thrombosis of the gallbladder, subcapsular hemorrhage, characteristic lesions of the hepatic artery and areas of hepatic necrosis and of lymphocytic infiltration. In his second case purulent material could be expressed from the liver, and there were hepatic and cholecystic arterial thromboses. Most interesting was the fact that portal fibrosis and foci of degeneration of a cirrhotic type were present.

Herrman's patient, studied by MacCallum, also showed lesions of atrophic cirrhosis.

In Ophuls' patient the usual arterial thromboses and secondary infarcted areas were scattered throughout the liver. The unusual feature was the presence of granulomatous nodules.

Kountz'<sup>33</sup> patient had icterus and also peripheral neuritis. The oldest lesions were present both in the arteries and in the veins of the gallbladder. The portal veins of the portion of the liver draining the gallbladder were most involved. It was this association which prompted the author to consider the gallbladder as the original focus in this syndrome with generalized dissemination.

Both of Singer's patients had icterus and pain and tenderness in the right upper quadrant of the abdomen, apparently explained by the periarteritic lesions of the gallbladder (one had cholelithiasis also).

In Gruber's 14 year old patient, with acute nephritis secondary to tonsillar abscesses, microscopic examination disclosed periarteritis nodosa limited to the gallbladder and liver. In another of his patients, with a history of the rheumatic state and grip, the clinical picture of cholecystitis developed. Duodenal drainage disclosed many leukocytes in the bile. Chills and fever occurred, and finally cholecystectomy was performed. On microscopic examination the gallbladder, which was thickened and shrunken, showed periarteritis nodosa. Pass,<sup>34</sup> in a study of infarction of the liver, observed that periarteritis nodosa was the most frequent cause, 22 of 170 cases of periarteritis nodosa were thus

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32 Plaut, A. Proc New York Path Soc **14** 13 (Nov.) 1931

33 Kountz, W. B. Periarteritis Nodosa, Arch Path **10** 55 (July) 1930

34 Pass, I. Infarction of the Liver, Am J Path **11** 503 (May) 1935

involved Schmorl's case of acute thrombosis of the portal vein with fatal termination is an example of a severe venous disturbance in the syndrome designated "arteritis"

The foregoing cases are examples of the variety of symptoms and of lesions of hepatic and cholecystic origin on the basis of periarteritis nodosa

Case	Hepatic Lesions	Original diagnosis
1	Hemorrhagic infarction	
4	Fatty degeneration, periarteritic nodules	
7	Hemorrhagic infarction	
9	Periportal fibrosis	Cholecystitis
13	Focal necrosis	
14	Acute periarteritis nodosa, acute periportal inflammation, polymorphonuclear leukocytes and bile thrombi within small ducts	
17	Fatty degeneration	

In our series such instances have been infrequent. Symptoms suggestive of cholecystitis occurred in case 9. Jaundice was present in case 14, in which the cholangitis in addition to the hepatic arteritis was noteworthy. Five patients presented arteritic lesions of the liver, 1 showed periportal fibrosis, and 2, fatty degeneration. However, symptoms attributable to hepatic impairment were unusual in these patients. Similarly, though the gallbladder was frequently involved, clinical indications of cholecystic involvement were rare.

Whether the report of cirrhosis of the liver with periarteritis nodosa represents anything more than an accidental association is difficult to say.

#### LESIONS OF THE ADRENAL GLANDS

Microscopic lesions of periarteritis nodosa were noted in the adrenal glands in cases 14 and 15 without any correlative clinical symptoms.

#### LESIONS OF THE CENTRAL NERVOUS SYSTEM

Involvement of the central nervous system in this syndrome has been considered rare, though peripheral neuritis was long included as an integral part of periarteritis nodosa and was present in association with the characteristic lesions of the nutrient arteries and occasionally with gliosis of the spinal cord. Twenty of Gruber's patients had peripheral neuritis, 9 had cerebral and meningeal involvement, and 2, lesions of the spinal cord. Hampel<sup>35</sup> reported a case in which the vascular lesions were limited to the meninges. The occurrence of a cerebral hemorrhage in a 10 year old girl with generalized periarteritis nodosa was reported by Kammenstiel. In this case there was the following sequence: otitis media, abdominal pain (for which appendectomy was performed, revealing the appendix to be normal), generalized convulsions and death.

<sup>35</sup> Hampel, E. Zwei ungewöhnliche Fälle von Periarteritis nodosa, Ztschr. f. d. ges. Neurol. u. Psychiat. **146** 355, 1933.

Bruckmann and Gerlach reported a case in which there were attacks of jacksonian epilepsy, which included unconsciousness and relaxation of the sphincters, in this syndrome In 1 patient the clinical diagnosis was tumor of the brain Bennett and Levine<sup>36</sup> recently described an instance of periarteritis nodosa involving cerebral and neural vessels, which clinically simulated chronic meningitis Vance and Graham<sup>37</sup> reported a case of generalized lesions, including the vessels of the brain, in a young adult Negro for whom the diagnosis was established at laparotomy

An analysis of our records shows that 8 patients had symptoms referable to the nervous system, 2 with peripheral neuritis In 6 the

TABLE 4—Data on Neurologic Observations

Case	Neurologic Symptoms	Postmortem Observations
1	Nuchal rigidity, positive Kernig sign	Intimal proliferation, occasional thrombosis, pigment laden gutter cells, circumscribed areas of mucinous degeneration, productive meningitis, diffuse gliosis of brain
4	Convulsions, transient amaurosis	Not examined
5	Nuchal rigidity, convulsions, transient amaurosis, "encephalitis"	Not examined
7	Nuchal rigidity, positive Kernig and Brudzinski signs	Edema of brain, diffuse gliosis, perivascular gutter cells, thickened vessels
11	Left ankle clonus, numbness of left hand, convulsions, nuchal rigidity, myoclonus, spontaneous hippus movement of pupils	Not examined
12	Peripheral weakness of left side of face, nerve deafness on right, similar involvement of nerves on left, Ramsay Hunt syndrome	Brain grossly normal except for enlargement of ventricles
16	Glovelike hyperesthesia—peripheral neuritis	Not examined
17	Bilateral ulnar neuritis, clouding of sensorium, polyneuritis, impairment of joint sense	Cortex of brain covered with gelatinous, edematous exudate underneath pia arachnoid, blood vessels moderately congested, perivascular infiltration with glia cells and fibrosis, occasional pigment laden gutter cells in perivascular space, hyaline changes in vessels

symptoms were interpreted as due to encephalomeningitis, and necropsy showed a productive perivascular and meningeal reaction In this connection it is interesting to recall Chvostek and Weichselbaum's patient who showed pupillary changes, rigidity of the neck and symptoms of encephalitis, which had been attributed to syphilis of the central nervous system

In a recent case, the first reported in Belgium,<sup>38</sup> the patient presented the clinical signs of meningitis, in addition to articular pains, and hemor-

36 Bennett, G A, and Levine, S A Two Cases of Periarteritis Nodosa, *Am J M Sc* **177** 853, 1929

37 Vance, B M, and Graham, J E Periarteritis Nodosa Complicated by Fatal Intrapericardial Hemorrhage, *Arch Path* **12** 521 (Oct) 1931

38 Van Bogaert, L, Stolz, B, and Ley, R A Sur une observation de periarterite noueuse a localisation neuro-cutanee, *Ann de méd* **31** 530, 1932

rhagic spinal fluid was obtained on several occasions. Improvement occurred, but in six months all the symptoms recurred and bloody spinal fluid was obtained, with the additional finding of hemorrhagic nodules grouped and distributed like the lesions of herpes zoster. Again a remission occurred, followed by a terminal recurrence in which there were diplopia, strabismus, automatic movements, massive lumbosacral purpura, gangrene of one great toe and xanthochromic spinal fluid. The diagnosis was established by means of biopsy of the skin.

Though major vascular accidents involving the central nervous system have been infrequent thus far in this disease, they may be anticipated, and it is likely that in some cases idiopathic subarachnoid hemorrhage is on this basis.

TABLE 5—*Lesions of Skin and Oral Mucous Membranes*

Case	
1	Purpura, erythematous maculopapules distributed diffusely
4	Blisters on tongue, swelling of face
5	Purpura of hip
6	Maculopapules on upper extremities, pulsatile nodules on face
7	Purpura in antecubital fossa
8	Scarlet fever followed by urticaria
11	Purpuric spots on back and pectoral region
12	Red swellings on legs, 5 cm. in diameter
13	Ulcerations of tongue and buccal mucosa, hemorrhagic skin lesions, fawn colored maculopapules on neck and trunk ("erythema multiforme associated with tuberculosis"), herpetiform lesions about mouth
14	Purpura
16	Postular and sanguineous rash over face (medicamentosa?), white centered petechiae on conjunctivae, shoulders and arms, erythematous macules on face, edema of ankles and eyelids
17	Papular rash of face (medicamentosa?), urticaria of left hypochondrium, petechial hemorrhages, swelling of face
Total	12 cases

## CUTANEOUS LESIONS

About 15 per cent of the patients reported on had cutaneous lesions. In 36 patients with cutaneous involvement studied by Alkiewicz,<sup>39</sup> the following types of lesions were present (some in combination): macules in 16 cases, nodules in 15, nodes in 11, extravasated blood in 7 and necrosis in 5.

Several cases have been reported in which the lesions were apparently restricted to the skin and subcutaneous tissues. Alkiewicz reported the case of a patient who for about two years presented chronic sepsis, with recurrent crops of nodes on the skin ranging from the size of a pea to that of a plum. These were slightly tender, dull red and slightly scaly. The areas were distributed irregularly over the extremities and back and became necrotic. Healing was slow and resulted in atrophy of the skin. No physical findings other than fever and facial edema

<sup>39</sup> Alkiewicz, J. Multiple nekrotisierende Periarteritis nodosa der Haut, Arch f Dermat u Syph **168** 522, 1933.

were noted Streptococci (unmentioned type) were cultivated from the necrotic areas, the blood cultures were sterile

Periarteritis nodosa limited to the skin has been noted following erysipelas<sup>11</sup> The patient was a 64 year old housewife with erysipelas of the forearm which lasted for one week In two months lentil-sized elevated nodules of the skin occurred at the site of the erysipelas The forearm was enlarged, though pitting edema was not present Slightly indurated macules and slight marmoration also were present Biopsy of the skin at this time showed pericapillary (arterial) and venous infiltration and typical fragmentation of the media elastica of the arteries Otherwise the patient has remained well

Lindberg<sup>40</sup> reported 2 cases of the disease with a long duration in which subcutaneous nodules were present The first patient, a young girl, had an infected wound of the foot complicated by articular pains and finally by the appearance of subcutaneous nodules Both the development and the subsidence of the nodules and of the severe constitutional symptoms were rapid Several attacks occurred, one after apparent influenza Biopsy and serial histologic examination showed segmental involvement of the subcutaneous vessels

The second instance occurred in a man of 50 with long-standing, inadequately treated syphilis Subcutaneous nodules appeared on the extensor surfaces of the extremities Biopsy showed aneurysmal dilatation of the small arteries

Matthes described pulsating subcutaneous nodules In the patient with the clinical course of recurrent meningitis, already referred to, the severity of the cutaneous lesions paralleled that of the general condition Thus the purpuric spots on one foot cleared and were followed by hemorrhagic nodules which were like the lesions of herpes zoster in their configuration and distribution In the fatal recurrence massive purpura of the lumbosacral region was present, together with gangrene of one great toe In addition to intracutaneous hemorrhage, biopsy of the skin disclosed typical arteritis, a homologous type of phlebitis and of pericapillary infiltration and also foci of the same cell constituents in relation to the cutaneous glands

In another recent case of periarteritis nodosa,<sup>41</sup> the second reported in France, the initial cutaneous lesion was a scarlatiniform rash on the abdomen, which became purpuric and progressed to vesicle formation with blood-tinged contents Superficial necrosis with blackened crusts was distributed over the tips of the ears, about the nares, at the tip of the chin and on the midportion of the mouth

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40 Lindberg, K Ueber eine subkutane Form der Periarteritis nodosa mit langwierigen Verlauf, Arb a d path Inst d Univ Helsingfors 7 159, 1933

41 Hutinel, J, Coste, F, and Arnaudet, A Periarterite noueuse de Kussmaul Bull et mem Soc med d hôp de Paris 54 46 (Jan 27) 1930

Thirteen patients in our series (76 per cent) had cutaneous lesions varying from transitory urticaria to ulcerative lesions. Urticaria, which is generally considered a cutaneous manifestation of an allergic state, has been noted in a few instances (our case 8, Lamb's case 1 and Ophuls' case). Actually, the significance of urticaria in the pathologic physiology of the blood vessels in this disease is not known. Edema with slow pitting, occasionally involving the face, has been observed several times. The variety of lesions listed in the accompanying table is striking. The resemblance to the pleomorphic lesions of erythema multiforme is evident. Erythema nodosum was the diagnosis made in the cases reported on by Klotz and Ophuls, and it was considered applicable

TABLE 6—*Ocular Findings*

Case	Ocular Findings	Renal Lesions	Miscellaneous
1	Retinal exudates, hemorrhages of retinal arteries	Glomerulonephritis	Hypertension
5	Perivaseculitis, hemorrhages of retinal arteries	Numerous minute renal infarcts	Hypertension
6	Neuroretinitis, fibrinous exudate of retina	Large renal infarcts, perirenal hematoma	Gradual increase in blood pressure
7	Obliterated disk margins, reddened disks, thin arteries, full veins, many exudates, few hemorrhages	Malignant nephrosclerosis	Hypertension before admission to hospital
9	Edema of retina and disk, complete amaurosis, no pupillary reaction to light	Renal infarctions	Hypertension
12	Edema of lids, chemosis of conjunctivae, episcleritis, iritis, normal fundi	Periarteritis nodosa of kidneys, renal hemorrhage	Hypertension
14	Thin, irregular retinal vessels	Arteriosclerosis	Senility
15	Papillitis, linear hemorrhages of retinal arteries, thin, irregular retinal arteries, old retinal exudates	Malignant sclerosis	Hypertension
17	No ophthalmoscopic findings	Renal infarctions, necrotic arterioles, proliferation of glomerular nuclei	Hypertension, "atypical verrucous endocarditis", choroidal periarteritis nodosa

in our case 12. The pathognomonic aneurysmal lesion occurred in only one instance (case 6). Particularly interesting was the occurrence of white-centered petechiae in case 16, a finding usually associated with bacterial emboli, though occasionally with atypical verrucous endocarditis (in which blood cultures are characteristically sterile). This finding has not been reported previously in connection with periarteritis nodosa. Attacks of scarlet fever and urticaria (case 8), of erysipelas and cutaneous nodules and of posttraumatic cellulitis (Gray<sup>42</sup>) preceding periarteritis nodosa seem significant.

Since the skin proper is preeminently a capillary bed and contains few arterioles, it is an excellent indicator for involvement of the capillary portion of the vascular tree in this syndrome.

42 Gray, cited by Rothstein and Welt<sup>16</sup>



## OCULAR INVOLVEMENT

The routine ophthalmoscopic examination disclosed definite signs in 6 cases. Periarteritis nodosa of the choroidal arteries was described for the first time by Goldstein and Wexler<sup>43</sup> (our case 17) with no ophthalmoscopic evidence. In our case 12 portions of the eye other than the fundi were involved. Even more extensive involvement—iridocyclitis, episcleritis, orbital cellulitis and arteritis of the choroidal vessels—was reported in a 10 year old child<sup>44</sup>. Isolated necrotizing, inflammatory lesions of the small choroidal arteries were noted by Helpern and Trubek<sup>45</sup> in a patient who had gonorrheal urethritis complicated by ophthalmia.

Typical nodular lesions in the short ciliary arteries have been described<sup>45a</sup>.

The only report of typical involvement of the retinal arteries was made by P. Muller in 1899, he described changes similar to those in the small vessels in the brain. However, no subsequent observer has reported such characteristic lesions of the retinal arteries.

Herrenschwand commented on the frequency of albuminuric retinitis in periarteritis nodosa. Histologic studies were made by Friedenwald and Rones<sup>46</sup> of albuminuric retinitis in a case of periarteritis nodosa with the ophthalmoscopic findings of edema of the retina and optic disk, with marked arteriosclerosis, hemorrhages and cotton-wool exudates. Histologically, the typical characteristics of albuminuric retinitis were present, the retinal vessels were sclerotic and lacked the lesions of periarteritis nodosa, which, however, involved the choroidal arteries.

These authors also described a case of healed syphilis and arteriosclerosis with nodules of inflammatory tissue related to sclerotic and partially thrombosed arterioles in the choroid. They cited this case as a connecting link between the vascular lesions of arteriosclerosis and those of periarteritis nodosa.

The retinal lesions in cases of periarteritis nodosa are such as have occurred in association with essential hypertension, malignant sclerosis,

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43 Goldstein, I, and Wexler, D. The Ocular Pathology of Periarteritis Nodosa, *Arch Ophth* **2** 288 (Sept) 1929.

44 Krahulik, L., Rosenthal, M., and Loughlin, E. H. Periarteritis Nodosa in Childhood with Meningeal Involvement, *Am J M Sc* **190** 308 (Sept) 1935.

45 Helpern, M., and Trubek, M. Necrotizing Arteritis and Subacute Glomerulonephritis in Gonococcal Endocarditis, *Arch Path* **15** 35 (Jan) 1933.

45a King, E. F. Ocular Involvement in Periarteritis Nodosa, *Tr Ophth Soc U Kingdom* **55** 246, 1935. King described a case in which the diagnosis of periarteritis nodosa was established by biopsy and in which papilledema with secondary atrophy developed in one eye and in the other eye recurrent iritis with secondary glaucoma which necessitated enucleation. Pathologic examination revealed intense subacute uveitis and retinal periarteritis.

46 Friedenwald, J. S., and Rones, B. Ocular Lesions in Septicemia, *Arch Ophth* **5** 175 (Feb) 1931.

glomerulonephritis and prolonged infections. In Gruber's series 14 patients showed changes in the fundi, all of which were associated with some renal lesion. All of our patients who came to necropsy showed renal involvement, about half of them having lesions of the fundi, as determined clinically.

Obviously, one may consider albuminuric retinitis as an expression of the renal disease as such or of the periarteritis nodosa. Since the renal lesions are intimately associated with periarteritis nodosa, the system disease, even though the renal arterioles may not show the typical lesions of periarteritis nodosa, the dilemma may be more apparent than real.

Both hypertension and narrowing of the retinal arterioles have been observed to develop during the clinical course of periarteritis nodosa. Retinal arteriolosclerosis seems to be one of the accompaniments of periarteritis nodosa.

#### POLYSEROSITIS

In 7 of the cases in which necropsy was performed polyserositis of varying extent was associated with periarteritis nodosa as illustrated in the following summary:

##### Case

- 1 Fibrinous pericarditis
- 4 Chronic peritonitis and pleurisy
- 8 Pleural, perihepatic and perisplenic adhesions, as noted at laparotomy, fibrinous exudate and edematous periduodenal tissue
- 9 Vascularization and thickening of the pericardium
- 10 Granular deposits in the pleurae
- 14 Adhesions in the right pleura, fibrinous granules and adhesions of the parietal pericardium
- 16 Serosanguineous fibrinous pleurisy and hydrothorax on the right
- 17 Pericardial adhesions and bullous edema of the visceral pericardium, a similar type of pleural involvement, thickened capsules of the liver and kidneys, peritoneal effusion

Similarly, Lamb's<sup>47</sup> 2 patients and Ophuls' patient had polyserositis. In Lamb's first patient asthma, urticaria and purpura were noted, and at postmortem examination fibrinous pleurisy, pericarditis and perisplenitis, as well as valvular vegetations and glomerulonephritis in all stages, were present. The second patient, who was considered to have appendicitis and pharyngitis, showed nephritis and arthritis postoperatively, and at postmortem examination there were effusions in the pleura, pericardium and peritoneum, periarteritis nodosa of the heart and kidneys, infarctions of the pancreas and a normal appendix.

Ophuls' patient also had symptoms treated by appendectomy and in several months showed subconjunctival hemorrhage, grossly bloody stools, asthmatic breathing and anasarca. At postmortem examination, in addition to the characteristic histologic picture of periarteritis nodosa, there were grayish nodules in the pleura, pericardium and myocardium. The nature of the nodules is extremely interesting; they had no distinct

<sup>47</sup> Lamb, A. R. Periarteritis Nodosa. A Clinical Pathological Review of the Disease, *Arch. Int. Med.* **14**: 481 (Oct.) 1914.

connection with the blood vessels, they were granulomatous and consisted of young vascular connective tissue, containing eosinophils, plasma cells and swollen endothelial cells. This type of reaction was noted also in relation to the veins, perivascular lymphatic vessels, bronchi, interstitial myocardium, lymph nodes and spleen. The first patient of Middleton and McCarter's<sup>48</sup> series presented symptoms suggesting partial intestinal obstruction, which were explained by the necropsy observation of fibrous adhesions about the gallbladder, cecum and pelvic portion of the small intestine, free peritoneal fluid and fibrinous exudate. In addition, pleural fluid, fibrous adhesions of the pericardium and pleura and even a patch of pericardial calcification were present. The third patient also had polyserositis.

TABLE 7—*Leukocyte Count*

Case	On Admission	Later	Polymorphonuclears, Percentage
1	17,000	36,000	90
2	28,000		80
3	39,000		96
4	20,000		80
5	40,000	12,000	90
6	36,000	54,000	75
7	35,000	16,650	86, 81
8	14,000	25,000	79, 80
9	12,000		94
11	14,000		80
12	18,400	12,000	85
		with 28% monocytes	
13	19,000		90
14	10,700		90
15	9,500		80
16	10,650		
	with 18% eosinophils		
17	10,200	6,580	87

Incidentally, our case 17 illustrates the transition from the effusive to the adhesive type of serositis. It will be recalled that though signs of fluid were present clinically and roentgenographically, no actual fluid could be obtained on aspiration.

One may infer that polyserositis is a tissue reaction in response to the underlying exciting agent analogous to the vascular reaction.

#### HEMATOLOGIC FINDINGS, TEMPERATURE AND PULSE RATE

Though leukopenia is occasionally present, leukocytosis is far more usual, counts of 40,000, 56,000 and 66,000 having been encountered relatively frequently. Such high leukocytosis is otherwise rare, sometimes occurring in lobar pneumonia.

The predominant cell type is the polymorphonuclear leukocyte, to the extent of 96 per cent. Striking eosinophilia has occurred in a minority of instances, the count being 23 per cent in Lamb's first case,

<sup>48</sup> Middleton, W. S., and McCarter, J. C. Diagnosis of Periarteritis Nodosa, *Am J M Sc* **190** 291 (Sept.) 1935.

79 per cent in Strong's<sup>49</sup> case and 18 per cent in our case 16. The eosinophilia may be transient, and it may disappear when some surgical complication occurs. In one instance (case 12) a monocyte count of 38 per cent was present, and a diagnosis of monocytic leukemia was made. The high leukocytosis is correlated only with a high percentage of polymorphonuclear cells.

An increase in the number of blood platelets occasionally occurs.

Secondary anemia of varying degree may be present. Because of hemosiderosis of the spleen, the anemia has been attributed to hemolysis (cited by Gruber).

The tourniquet test has been positive in some instances.

No changes in the coagulability of the blood and in the bleeding time have been recorded.

By far the greater number of our patients showed the septic type of temperature curve, in a few the temperature was subfebrile or normal.

The pulse has been rapid.

#### HEALING IN PERIARTERITIS NODOSA

A number of instances of healing and of prolonged remissions in the course of this malady are on record. Erlandsson's<sup>50</sup> patient died one year after the diagnosis had been established by biopsy and had no lesions at postmortem examination (death was due to metastases from a carcinoma of the uterus).

Lindberg's<sup>40</sup> first patient with periarteritis nodosa of the subcutaneous type was sick for four years, and at the time of the publication of the case report he had been entirely well for one year. The patient reported on by Carling and Braxton-Hicks<sup>51</sup> had apparently recovered. Benedict's patient<sup>52</sup> was alive one year after the diagnosis had been established by biopsy of a subcutaneous nodule. At the later date only two nodules remained. Von Haun's<sup>53</sup> patient with subcutaneous nodes and fever was discharged to continue army service. Schottstaedt<sup>54</sup> reported a remission in a patient with cutaneous periarteritis nodosa, in these patients there was no evidence of nephritis in the urine.

49 Strong, G. F. Periarteritis Nodosa, *Canad. M. A. J.* **19** 534, 1928.

50 Erlandsson, S. Neurologische Krankheitsbilder bei Periarteritis nodosa, *Acta psychiat. et neurol.* **6** 369, 1931.

51 Carling, E. R., and Hicks, J. A. B. Periarteritis Nodosa, Accidentally Recognized During Life, *Lancet* **1** 1001, 1923.

52 Benedict, H. Ueber Periarteritis nodosa, *Ztschr. f. klin. Med.* **64** 405, 1907.

53 Von Haun, F. Pathologische-histologische und experimentelle Untersuchungen über Periarteritis nodosa, *Virchows Arch. f. path. Anat.* **227** 90, 1920.

54 Schottstaedt, W. Case of Periarteritis Nodosa with Remission of Symptoms, *California & West Med.* **36** 186, 1932.

Nephrectomy was performed on a woman because of renal hemorrhage due to aneurysm, she was alive and apparently well several years after the operation (Powell and Pritchard)

The patient of our series who was reported on by Manges and Baehr<sup>4</sup> had pulsatile nodules on the face, but by the time of her second admission to the hospital they had disappeared. Biopsy of a mesenteric artery during laparotomy at the onset of the disease revealed a cellular inflammatory lesion of the vessel wall. Later in the course of the disease biopsy of a branch of the temporal artery revealed a healing but cellular lesion. At necropsy most of the lesions consisted of irregular scars or degenerated areas in the vessel walls, chiefly in the media.

One patient with periarteritis nodosa was alive twenty-five years after the diagnosis had been made (cited by Alkiewicz). Three or 4 more instances might be cited. Perhaps time will permit the condition in our cases 2 and 3 to be demonstrated as arrested periarteritis nodosa.

The prognosis, thus, is not absolutely fatal but depends, among other factors such as toxemia, on the extent of the vascular involvement and on the importance of the impaired organs.

#### THE ERYTHEMA GROUP WITH VISCERAL MANIFESTATIONS IN RELATION TO PERIARTERITIS NODOSA

Case 1, in which the condition was first considered as belonging to the erythema group of Osler, is noteworthy because the apparent error may serve as a clue to the solution of this heterogeneous syndrome. The pathologic substratum of Osler's disease, as summarized by Christian,<sup>55</sup> is a focal disturbance in the small blood vessels—capillary, precapillary and postcapillary—which causes dilatation, diapedesis and exudation either singly or in combination. Actually, pathologic material is inadequate. Thus, there is a report by MacCallum and Watson on one of Osler's patients who died in uremia and in whom subacute glomerulonephritis was observed. There is also a report by Trimble<sup>56</sup> of a case in which the appendix was hemorrhagic and gangrenous. Few other references have been found. It seems significant that the papers on the Osler erythema group have appeared only in English, suggesting that studies of this syndrome have been made from a different approach, perhaps from the standpoint of the clinician rather than of the pathologist.

On considering the erythema group with visceral crises, it is found that the condition is diagnosed fairly often clinically and inadequately

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55 Christian, H. Visceral Disturbances in Patients with Cutaneous Lesions of the Erythema Group, *J A M A* 69 325 (Aug 4) 1917

56 Trimble, I R. Erythematous Group of Skin Diseases with Especial Reference to Abdominal Pain, *J A M A* 96 2010 (June 13) 1931

studied pathologically, whereas in periarteritis nodosa the reverse has been true in the past. Indeed, Osler's emphasis on the admittedly miscellaneous collection of patients with "visceral manifestations of the erythema group" and his prophetic statement in 1914<sup>57</sup> in regard to the "anaphylactic" mechanism on either an infectious or metabolic basis, is strikingly similar to Gruber's conception of periarteritis nodosa, which, to repeat, is not that of a unitary disease but of a peculiar hyperergic expression of sensitized portions of the arterial wall of one or several organs in the course of some usually prolonged infection or septic disease.

The clinical resemblance between these two syndromes, with their varying manifestations, is remarkable when one rereads Osler's<sup>58</sup> case reports and tentatively applies the diagnosis of periarteritis nodosa to them. For example, Osler's twentieth patient, a boy of 15, had an attack of severe colic and was admitted to the hospital for suspected appendicitis. In a week a purpuric erythematous eruption appeared on the legs, with acute nephritis and melena. The patient recovered. In other cases (cases 21 and 29) the condition apparently followed an acute infection, such as otitis media. In case 26, that of a woman aged 24, there were erythema, urticaria and purpura, a chill, followed by consolidation of the lower portion of the left lung with delayed resolution, enlargement of the lymph nodes and thrombosis of the femoral vein. There was gradual recovery, with subsequent acute nephritis and death in uremia. Seven of Osler's original patients died in uremia. Clinically, the vascular involvement was certainly greater than the capillary lesions suggested by Christian as the cause of Osler's syndrome.

The characteristics of the erythema group are also descriptive of periarteritis nodosa: (1) polymorphous lesions of the skin, which may be acute, circumscribed edema, urticaria, purpura or ordinary exudative erythema, (2) polymorphous visceral lesions—local serous hemorrhagic exudate in the gastro-intestinal tract causing crises of pain and hemorrhages, acute nephritis and certain rare pulmonary and other lesions, and (3) infiltration of the synovial sheaths, periauticular tissue and joints.

In 3 of Christian's 10 patients with the erythema group, the condition was thought to have been due to food sensitivity, in 2 it followed a sore throat, in 1 it was associated with a positive Wassermann reaction, and in 1, in whom there were purpura, abdominal pain, hematuria, melena and recurrent arthritis and fever, it occurred in the course of diffuse miliary tuberculosis, and at postmortem examination the kidneys

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57 Osler, W. Purpura with Visceral Lesions, *Brit M J* **1** 517, 1914.

58 Osler, W. On the Visceral Manifestations of the Erythema Group of Skin Diseases, *Am J M Sc* **127** 1 (Jan) 1904.

were slightly enlarged, with small hemorrhagic foci of intertubular and intratubular distribution but without nephritis

The clinical similarity of the erythema group with a septic or infectious component to periarteritis nodosa is inescapable, despite the fact that a common pathologic lesion or factor has not been demonstrated

Osler pointed out the clinical resemblance, probably amounting to identity, between the erythema group and the Schonlein-Henoch group Pratt<sup>59</sup> was impressed with the similarity between the Schonlein-Henoch group and Franck's capillary toxicosis

On considering Schonlein-Henoch's purpura, one finds a similar lack of well studied pathologic material and a resemblance of clinical manifestations Hemorrhages into the serosa and mucosa of the intestine are common and are the cause of abdominal symptoms Dilated, lengthened, distorted capillaries have been observed in vivo The syndrome has been described in epidemic form suggesting an infection<sup>60</sup> It is of interest that in Lamb's first case of periarteritis nodosa the original diagnosis was purpura rheumatica

An allergic etiology, both on an infectious and on a metabolic basis, also has been suggested frequently for Schonlein-Henoch's disease, just as for the erythema group, on speculative clinical and experimental grounds The typical phenomena of the abdominal form were compared by Glanzmann<sup>61</sup> with those produced anaphylactically in dogs Descriptions of Schonlein-Henoch's disease show a resemblance to those of the clinical aspects of periarteritis nodosa, especially in regard to hemorrhagic perforation of the gastro-intestinal tract and nephritis<sup>62</sup> Unfortunately, no detailed report of the condition of the blood vessels has been found

It seems that capillary lesions with a tendency to spontaneous recovery are most characteristic of the erythema and purpura rheumatica group, though larger vessels also have been involved In distinction, the patients with this condition who ultimately proved to have periarteritis nodosa showed progressive and irreversible vascular damage involving generally the just visible arterioles principally, though also capillaries and veins

It is not intended to reduce the three syndromes to the same common denominator solely on the basis of their protean symptoms but to abstract

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59 Pratt, J H Purpura and Hemophilia, in Osler, W, and McCrae, T Modern Medicine, Philadelphia, Lea & Febiger, 1927, vol 5, chap 3, p 117

60 Morawitz, P, and Denecke, G Blut und Blutkrankheiten, in von Bergmann, G, and Staehelin, R Handbuch der inneren Medizin, Berlin, Julius Springer, 1926, vol 2, p 262

61 Glanzmann, E Beitrage zur Kenntnis der Purpura im Kindesalter, Jahrb f Kinderh **83** 271 and 379, 1916

62 Goldstein, E Schonlein-Henoch's Purpura, M Clin North America **12** 869 (Nov) 1928

from the instances of the erythema group those cases in which there were definite pathologic characteristics of the more accurately known periarteritis nodosa. The three syndromes—Osler's erythema group, purpura rheumatica abdominalis and periarteritis nodosa—have similar clinical manifestations, probably the same types of causative mechanisms, and certainly in some instances, as in our case 1, the same pathologic lesions.

TABLE 8—*Bacteria Associated with Periarteritis Nodosa*

Author	Source	Organism
Bomhard and Oberndorfer	Renal and splenic vessel	Staph aureus
Gruber's review		
Lamb, case 2	Peritoneal fluid Cardiac nodule	Staph aureus Varied organisms including streptococcus
Klotz, case 2	Heart blood Subcutaneous nodule Gallbladder and hepatic vessels and bile	Streptococcus Staph aureus, diphtheroid Staphylococcus and streptococcus
Klotz, case 1	Gallbladder bile	Streptococcus mitis
Beitzke		Streptococcus
Jonas, one case	Kidney Adrenal glands	Streptococcus Influenza bacillus
Lamb, case 1	Peritoneal fluid Neurotic lymph node Heart blood	Streptococcus Streptococcus Streptococcus
Beattie and Douglas	Kidney	Streptococcus
Gruber	Tonsillar abscess	Streptococcus
Ophuls	Pericardial fluid Blood culture	Diplostreptococcus Streptococcus in flask
Sternberg	Pulmonary vessels	Diplostreptococcus
Helpert and Trubek	Pulmonary valve	Gonococcus
Herrman	Blood culture Heart blood Spleen	Sterile Staphylococcus Streptococcus (neeropsy diagnosis streptococcus septicaemia)
Manges and Baehr	Tonsils	Str haemolyticus
Van Bogaert, Stolz and Lev	Sputum	Bacillus Friedlanderi
Alkiewicz	Skin ulcer Blood culture	Streptococcus Sterile
Hutinel, Coste and Arnaudet	Pulmonary nodule (post mortem)	Staph aureus
Moolten	Spinal fluid	Meningococcus

## THE ETIOLOGIC FACTORS

The bacteriologic observations in our cases were few and varied and will therefore be considered in conjunction with those of previous observers, though there are limitations to a consideration of data obtained from numerous sources.

In no instance has the rôle of some filtrable virus been other than conjectural.

Only 6 of Gruber's collection of patients through 1925 showed positive bacteriologic evidence. Including subsequent cases, the organism most frequently isolated was the streptococcus and then the staphylococcus, in single instances, the influenza bacillus and the gonococcus, respectively, were obtained. In 1 patient, previously referred to<sup>41</sup>



(with persistent diarrhea and rash varying from the scarlatiniform to gangrene), a seropurulent vaginal discharge was present, from which streptococci were obtained, on postmortem examination the lungs and the liver each contained a small abscess with staphylococcic pus. The etiologic importance of these bacteria could not be evaluated. Several injection experiments in animals were inconclusive.

The rôle of the gonococcus in the evolution of the disease was clearly determined in one instance (in the case reported by Helpern and Trubek). The organism was recovered at autopsy from the pulmonary valve of the patient, who had shown a development from gonococcic urethritis to subacute gonococcic endocarditis and finally to the microscopic characteristics of necrotizing arteritis and glomerulonephritis. This is the clearest example of a relationship between periarteritis nodosa and an infectious state.

In one recent case of proved and treated meningococcic meningitis in a previously healthy girl of 10 years the condition was complicated by arthralgia, abdominal pain and melena, which suggested the diagnosis of periarteritis nodosa, which was confirmed.<sup>63</sup>

The relation of *Str. haemolyticus* to the development of periarteritis nodosa is more inferential, partly because this organism is associated with a variety of disease entities. It appears as the essential bacterial factor in the prodromal illnesses of periarteritis nodosa, for instance, in acute tonsillitis (3 of our cases, Lamb's second case, both of Klotz' cases and in some of Gruber's cases), in scarlet fever (in our cases 8 and 10), and in erysipelas preceding the development of periarteritis nodosa at the site of the lesion.<sup>11</sup>

In a study of 165 cases of streptococcus sepsis Sigmund<sup>64</sup> found that one fifth of the patients had mycotic aneurysms apparently due to purely degenerative lesions of the vessels, some of the lesions closely resembled those of periarteritis nodosa but lacked the gross aneurysms. Different stages of vascular reaction were observed in experimental animals and were attributed to the particular state of immunity.

The impression has been strengthening that the rheumatic state is related to the syndrome of periarteritis nodosa. It has been suggested by Oskar Klotz, on the basis of clinical correlation, that periarteritis nodosa may be a vascular reaction occurring in the course of rheumatic fever and rheumatoid infections. Such a correlation is present in our cases 1, 8, 10 and 15, in which fresh Aschoff bodies and verrucous endocarditis were present and typical acute periarteritis as well. These have been reported in an article entitled "Periarteritis Nodosa (Necrotizing

63 Moolten, Sylvan. Personal communication to the author.

64 Sigmund, H. Gefassveränderungen bei chronische streptokokken Sepsis, Centralbl f allg Path u path Anat **35** 276, 1924.

Arteritis) Associated with Rheumatic Heart Disease" by Friedberg and Gross<sup>65</sup> Neale and Whitfield (cited by Middleton and McCartei<sup>68</sup>) reported a case of chorea in a child treated with salicylates in which a similar association of rheumatic lesions and periarteritis nodosa occurred

Besides this group of cases in which there were unmistakable lesions both of rheumatic fever and of periarteritis nodosa, there are some considered to be instances of rheumatic fever in which the condition seems to be associated with the erythema group of cutaneous diseases In some of these cases, reported by Schloss<sup>66</sup> under the title "Association of Rheumatic Fever and the Erythema Group of Skin Diseases," such varied and atypical symptoms were presented as to suggest the clinical course in some of our cases of periarteritis nodosa The pathologic involvement in this group was incompletely studied

Coburn<sup>67</sup> has reported another type in which critical abdominal symptoms occurred in association with acute rheumatic fever In a child sudden death followed an abdominal crisis In addition to Aschoff bodies and valvular lesions, hemorrhages from serous membranes, pulmonary alveoli, ovaries and along the colonic vessels were present (Coburn's case 1) In another case (Coburn's case 7) symptoms suggesting appendical abscess following grip were found on laparotomy, to be explained by necrosis of peritoneal fat and were followed by pancarditis, polyarthritis, pleurisy, hematuria and melena The appendix contained slightly dilated subserous vessels and clotted blood attached to the serosal surface In his case 8 hemorrhagic appendicitis was followed by migratory polyarthritis and rheumatic carditis

Coburn emphasized the fact that the condition is characterized by hemorrhagic lesions, which do not, however, depend on a specific change in the blood vessels and are not the accepted rheumatic lesion, though they frequently accompany typical endocardial involvement The clinical observation has been made that patients with rheumatic fever who have abdominal symptoms are most likely to have associated periarteritis nodosa

For the purpose of demonstrating a relationship of rheumatic fever to periarteritis nodosa, it has seemed tenable to grade the syndromes as follows (1) those with the typical symptoms of rheumatic fever, (2) those disseminated symptoms suggesting the erythema group clinically,

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65 Friedberg, C. K., and Gross, L. Periarteritis Nodosa (Necrotizing Arteritis) Associated with Rheumatic Heart Disease, *Arch Int Med* **54** 170 (Aug.) 1934

66 Schloss, O. Association of Rheumatic Fever and the Erythema Group of Skin Diseases, *Am J M Sc* **140** 226, 1910

67 Coburn, A. Factor of Infection in the Rheumatic State, Baltimore, Williams & Wilkins Company, 1931

(3) those with symptoms based on hemorrhagic vascular lesions which are neither specifically rheumatic nor typical of periarteritis nodosa and (4) those with the typical lesions of both syndromes and a variegated clinical picture

Syphilis is not intimately related to periarteritis nodosa. In one recent case, periarteritis nodosa occurred in a syphilitic patient who was inadequately treated but who showed a serologically negative reaction (Lindberg). However, Jacobsen<sup>67a</sup> recently reported 2 cases of periarteritis nodosa associated with clinical and serologic evidence of syphilis in which an autopsy was performed.

Vascular lesions, especially thrombosing arteritis, which occur in the more severe forms of some specific infections—pneumonia, influenza, epidemic meningitis and secondary syphilis—may be one predisposing factor in the development of periarteritis nodosa.<sup>68</sup>

The fact that an infection so frequently precedes the onset of periarteritis nodosa within the course of a few months suggests that an etiologic relationship exists between the two conditions.

As has already been mentioned, experimental attempts to reproduce the disease by means of inoculation and subinoculation of crushed nodules have been inconclusive. Metz in 1931 produced lesions of the periarteritic type but without aneurysms in rats which were first sensitized to streptococci and then given injections either of these organisms or of nonspecific serum. Gerber<sup>69</sup> produced vascular lesions, including necrosis of the walls, thrombosis and hemorrhage, in various viscera in kittens by means of repeated intravenous injections of bacterial toxins. Also, in some animals preliminary preparation with an intradermal as well as an intravenous injection seemed to favor development of systemic vascular lesions. This experimental work suggests the susceptibility of blood vessels to repeated exposure to bacterial products.

The allergic state in its most characteristic clinical form is exemplified in case 16. The first clinical indications occurred in this patient at the age of 35 and consisted of attacks of asthma. Positive results of cutaneous tests to flour, barley and feathers were obtained in the patient, who was a baker. The asthma continued to be a prominent symptom in addition to the diarrhea, peripheral neuritis and cutaneous lesions. At necropsy two years after the onset, numerous pulmonary infarctions

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67a Jacobsen, V. C. Periarteritis Nodosa, with Report of Two Cases Associated with Clinical Syphilis, in *Medical Papers Dedicated to Henry Asbury Christian*, Baltimore, The Waverly Press, Inc., 1936, p. 820.

68 Harbitz, F. Unknown Forms of Arteritis with Special Reference to Their Relation to Syphilitic Arteritis and Periarteritis Nodosa, *Am J M Sc* **163** 250 (Feb.) 1922. Derick, C. L., and Hass, G. M. Diffuse Arteritis of Syphilitic Origin, *Am J Path* **11** 291 (March) 1935.

69 Gerber, cited by Baehr, Klemperer and Schiffrin<sup>73</sup>

due to small thrombosed vessels were present which might be held accountable for the asthma. May allergy on a nonbacterial basis be associated with the development of periarteritis nodosa?<sup>69a</sup>

There is evidence pointing to the conception that glomerulonephritis with its associated vascular involvement is dependent on a mechanism of sensitization to a preceding disease which generally is of bacterial origin. (To cite this evidence briefly,<sup>69b</sup> glomerulonephritis complicating scarlet fever or tonsillitis develops when the primary disease has apparently receded, clinical symptoms which are extremely suggestive of glomerulonephritis occur in the course of serum sickness and of uterine attacks, glomerulonephritis has been noted to occur in one third of the cases of Libman's bacteria-free and healed stages of subacute bacterial endocarditis and in only 1 per cent of the cases during the bacteremic phase, glomerulonephritis occurs<sup>70</sup> occasionally in the course of protracted infections associated with the gonococcus, pneumococcus, meningococcus and influenza bacillus, glomerulonephritis is claimed to have been produced successfully in animals immunized against streptococci and not in those unimmunized. Richet<sup>71</sup> described symptoms of glomerulonephritis in the course of an allergic reaction to horse dander. Acute nephritis may occur in the Schonlein-Henoch syndrome, either as part of the attack or in the course of the patient's life.)

Glomerulonephritis is frequently enough associated with periarteritis nodosa. Lamb's first patient had glomerulonephritis in all stages. Indeed periarteritis nodosa has occasionally presented the clinical course of glomerulonephritis, as in Damblé's<sup>72</sup> case, that of a 7 year old girl and in our cases 1, 4 and 17. Damblé raised the obvious question of their etiologic relationship.

Clinically, in cases in which the final diagnosis is glomerulonephritis the condition often suggests Osler's erythema group, not because of the heterogeneity of symptoms but because of the other evidences of vascular injury. For example, a 36 year old man with previously known albuminuria had a severe attack of acute tonsillitis, followed in several weeks by arthritis, purpura, pitting edema of the lower extremities and

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69a Since the submission of this paper an interesting report of 3 cases in which the classic allergic symptoms were correlated with periarteritis nodosa has appeared (Cohen, M. B., Kline, B. S., and Young, A. M. The Clinical Diagnosis of Periarteritis Nodosa, *J. A. M. A.* **107** 1555 [Nov. 7] 1936).

69b Fishberg, A. M. Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1931, p. 355.

70 Baehr, G. Glomerular Lesions of Subacute Bacterial Endocarditis, *Am. J. M. Sc.* **44** 327, 1912.

71 Richet, C., and Dublineau, J. Le purpura rhumatoïde de nature anaphylactique, *J. méd. franç.* **19** 182 (May) 1930.

72 Damblé, K. Beitrag zur Pathologie der Periarteritis nodosa, *Beitr. z. path. Anat. u. z. allg. Path.* **85** 619, 1930.

definite evidence of glomerulonephritis—an association of symptoms which clinically suggested Osler's disease. Our first patient with periarteritis nodosa gave a similar history.

Glomerular lesions,<sup>73</sup> occasionally to the extent of true diffuse glomerulonephritis, have been noted in patients with vascular disease associated with lupus erythematosus and endocarditis which may be etiologically related to periarteritis nodosa.

In glomerulonephritis associated with periarteritis nodosa one may tentatively assume that there are two manifestations of vascular sensitization, which, if considered as being independent of each other, would be improbable. Until disproved, it is fair to assume with Gruber that glomerulonephritis is a local reaction to the causative sensitizing agent of periarteritis nodosa. Because of involvement of the capillaries and pericapillary inflammatory cells, a clinical expression different from that when the medium-sized vessels are injured is produced.

Keegan<sup>74</sup> reported a case in which one kidney was removed at laparotomy because of a gross appearance suggesting milary tuberculosis. These lesions proved to be those of periarteritis nodosa. The patient died two months later of renal insufficiency, and the other kidney showed early signs of arteriosclerosis and chronic vascular nephritis, apparently "healed" periarteritis nodosa. The relation of arteritis to renal disease, especially when localized to the kidneys, as in Fishberg's<sup>69b</sup> case, is convincing and recalls Jager's thesis that healed periarteritis nodosa may terminate in lesions closely resembling arteriosclerosis, particularly in relatively young persons.

In the so-called malignant phase of essential hypertension the etiology and pathogenic factors are conjectural. It has been suggested that there is a congenital predisposition in the vessels, that this is an accelerated form of arteriosclerosis and that lead or syphilis may be concerned. The vascular changes in the kidney, besides the arteriosclerosis, are necrosis, endarteritis, thrombosis and periarterial cellular infiltration of the renal arterioles. Fahr<sup>75</sup> stated that a sharp distinction cannot be drawn between the necrotizing arteriolitis of the kidneys in malignant sclerosis and the extrarenal lesions of periarteritis nodosa. Clinically, it seems that, as with glomerulonephritis, the occurrence of the two is fundamentally related.

Periarteritis nodosa, in the strict sense of the nomenclature, can apply only to the final degree of disruption of the walls of arterioles

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73 Baehr, G., Klemperer, P., and Schiffman, A. A Diffuse Disease of the Peripheral Circulation (Usually Associated with Lupus Erythematosus and Endocarditis), *Tr. A. Am. Physicians* **50** 139, 1935.

74 Keegan, J. J. Primary Vascular Nephritis or Renal Periarteritis Nodosa, *Arch. Int. Med.* **36** 189 (Aug.) 1925.

75 Fahr, cited by Gruber.<sup>9</sup>

which have been the seat of a necrotizing inflammatory process. In a wider and probably more accurate sense periarteritis nodosa is part of a profound systemic response to infections of diverse types or possibly even to metabolic factors. The striking perivascular lesions themselves indicate the susceptibility of the component tissues of the blood vessels. For the present it is the relation of periarteritis nodosa to other vascular diseases and the analysis of their etiologic factors which deserve further elaboration.

#### SUMMARY

Fifteen cases of periarteritis nodosa with postmortem studies are presented.

More than half the patients had prodromal illnesses—acute tonsillitis, acute sinusitis, scarlet fever or sensitization asthma. Four had had rheumatic fever.

The usual mode of onset was with abdominal pain, associated with articular, cardiac or renal symptoms.

All the patients showed cardiac involvement. Twelve had lesions of the coronary arteries of varying degree, 4 had Aschoff bodies. One clinically presented the characteristics of the indeterminate type of verrucous endocarditis. Periarteritis nodosa may be a superimposed vascular reaction in the course of rheumatic fever.

Periarteritis nodosa of the pulmonary arteries was present in 5 cases, in 6 there were pulmonary lesions not immediately dependent on arteritis. Pleural pain, asthma or typical bronchopneumonia may be the clinical manifestation. The roentgen findings suggested bronchopneumonia or small pleural effusions.

All the patients who came to necropsy showed renal involvement, principally renal infarctions and aneurysms, and acute periarteritis nodosa. Three had glomerulonephritis, 2 had malignant sclerosis. These lesions may indicate a reaction involving blood vessels of different sizes but otherwise equivalent to the usual lesion.

Seven patients had surgical complications involving the gastrointestinal tract. Periarteritis nodosa was the cause of hemorrhagic pancreatitis in 3 cases. Three patients had periarteritic involvement of the appendix. Isolated lesions of "necrotizing arteriolitis" resemble histologically periarteritis nodosa without the clinical course of the latter.

Hepatic and cholecystic lesions secondary to periarteritis nodosa were infrequent in our series. Five patients had arteritic lesions of the liver, 1 had periportal fibrosis and 2 had fatty degeneration. Instances of associated cirrhosis have been noted.

Eight patients had neurologic symptoms, in 6 there was a clinical impression of encephalomeningitis. The lesions were due to productive perivascular and meningeal reactions.

A variety of cutaneous lesions were present in 12 patients, such as erythematous maculopapules, purpura, urticaria, herpes, edema, pulsatile nodules and white-centered petechiae. It is suggested that the smaller branches of the circulation are involved similarly to the arterioles.

Retinal exudates, neuroretinitis and thinning of the retinal arteries were noted in association with a variety of renal lesions in the course of periarteritis nodosa but in themselves were not pathognomonic. One patient showed a characteristic nodule of the choroid on microscopic examination.

Twelve patients had polyserositis, which is interpreted as a reaction of the serous membranes to the cause of periarteritis nodosa.

A leukocyte count as high as 54,000 may occur. The predominant cell type is the polymorphonuclear leukocyte, though striking eosinophilia and an instance of monocytosis have been noted.

Healing and prolonged remissions were noted, especially in patients without nephritic manifestations.

Some patients with the erythema group on further progress have proved to have periarteritis nodosa. It is suggested that similar clinical manifestations and mechanisms and occasionally the same pathologic lesions are present in these syndromes.

One case has been recorded in which the development from gonococcal urethritis to subacute gonococcal endocarditis and finally to the microscopic characteristics of necrotizing arteritis and glomerulonephritis was observed. Periarteritis nodosa complicating meningococcal meningitis has recently been observed. The bacteria principally implicated in the prodromes of periarteritis nodosa are the hemolytic streptococci. One patient in our series showed typical manifestations of an allergic state about two years before periarteritis nodosa was evident, and clinically the two conditions merged.

# CARDIAC OUTPUT IN POLYCYTHAEMIA VERA

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Determinations of the cardiac output have not often been made in cases of polycythaemia vera. Early workers, who used unreliable methods, reported no marked deviation from normal. In 1925 Liljestrand and Stenstrom<sup>1</sup> found that the cardiac output was 10 per cent below normal in one case, the patient had a low basal metabolic rate (85 per cent of normal). The concentration of hemoglobin was 135 per cent, and the erythrocytes numbered 6,800,000 per cubic millimeter of blood. There was no enlargement of the spleen. The blood volume apparently was not determined. Ernst<sup>2</sup> in 1930 reported a cardiac output 10 per cent above normal in a case in which there was a 10 to 15 per cent increase in the basal metabolic rate. A diagnosis of polycythaemia vera was not warranted in this case, as the total blood volume, instead of being increased, was low, only 70 cc per kilogram of body weight. Relative polycythemia was present, as shown by the value for hemoglobin, by the erythrocyte count and by the percentage of cells as determined with the hematocrit. The spleen was not palpable. Grollman<sup>3</sup> stated that studies of the cardiac output in a few additional cases have shown a variation of  $\pm 10$  per cent from normal, but he gave no data. No further reports have been found in the recent literature.

In the following case of polycythaemia vera all the classic features of the disease were present: an increased number of erythrocytes, an elevated value for hemoglobin, a high percentage of cells as determined with the hematocrit, a markedly increased total volume of blood, a palpable spleen, the characteristic congestive appearance of the skin and a history of venous thrombosis. Studies were conducted at intervals over a period of eight months, during which time treatment with

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\* Now residing in New Orleans

1 Liljestrand, G, and Stenstrom, N. Clinical Studies on the Work of the Heart During Rest. II. The Influence of Variations in the Haemoglobin Content on the Blood Flow, *Acta med Scandinav* **63** 130-131, 1925.

2 Ernst, Curt. Beitrag zur Frage des Kreislaufes bei der Polycythaemia vera, *Ztschr f klin Med* **114** 757-764, 1930.

3 Grollman, Arthur. The Cardiac Output of Man in Health and Disease, Springfield, Ill, Charles C Thomas, Publisher, 1932.



phenylhydrazine was carried out. For determinations of cardiac output the acetylene method of Grollman<sup>4</sup> was used, each test being made under basal conditions.

#### REPORT OF CASES

CASE 1—A married woman of Swedish descent, aged 53, came to the clinic on Aug 7, 1933, complaining of weakness, loss of weight and purplish red face and hands. She had had influenza ten years before and had undergone appendectomy at the age of 23. She had five children, one of whom had diabetes, a sister was anemic and took liver. In 1929 she had first noticed that the hands and face became bluish on exposure to cold and became red and flushed in a warm atmosphere. The tongue and mouth had been purplish red. She had reached the menopause in 1930 and had had hot flashes for two years. Since 1930 tinnitus had been a constant symptom. In August 1932, after an attack of severe pain in the left upper portion of the abdomen, the spleen was found to be enlarged. About the same time thrombosis of one of the superficial veins of the left leg occurred. In the three years prior to her admission to the clinic the patient had lost 67 pounds (30.4 Kg), and for nine months weakness had forced her to remain in bed. In the year prior to her admission to the clinic she had noticed frequent palpitation, dizziness and slight pain in the thorax. Anorexia, flatulence and chronic constipation had been prominent complaints.

On physical examination the patient was markedly emaciated. Her height was 5 feet and 3 inches (160 cm), and she weighed 83 pounds (37.6 Kg). The skin of the face, especially across the nose and cheeks, and the lips, tongue, tips of the fingers and nail beds were a pronounced reddish blue. The blood pressure was 100 systolic and 70 diastolic, and the pulse rate was 90 beats per minute. The lymph nodes in the neck, axillae and groin were palpable. The veins of the legs showed marked varicosities, and those of the abdomen were dilated. The fingers were slightly clubbed. The heart and lungs were apparently normal. The spleen was markedly enlarged, extending below the umbilicus. A small umbilical hernia was present. Ophthalmoscopic examination revealed marked venous dilatation and a cyanotic appearance of the fundi. A diagnosis of polycythaemia vera was made as a result of the foregoing findings and the laboratory studies.

The patient was hospitalized, and treatment with phenylhydrazine was instituted. By August 18 17 Gm of phenylhydrazine hydrochloride had been administered, and the urine showed evidence of considerable destruction of blood. At this time splenic infarction and diaphragmatic pleurisy developed, so medication was temporarily discontinued. On August 24 acute thrombophlebitis of the varicosities of the right leg developed, accompanied with moderate pain. Medication was resumed on August 26, another 17 Gm of phenylhydrazine being given by September 3. No other untoward symptoms appeared during the patient's stay in the hospital, and she was dismissed on September 27 on a maintenance dose of 0.3 Gm of phenylhydrazine hydrochloride once a week. By this time she had gained 7 pounds (3.2 Kg) and was feeling much improved, and the hematologic findings were normal.

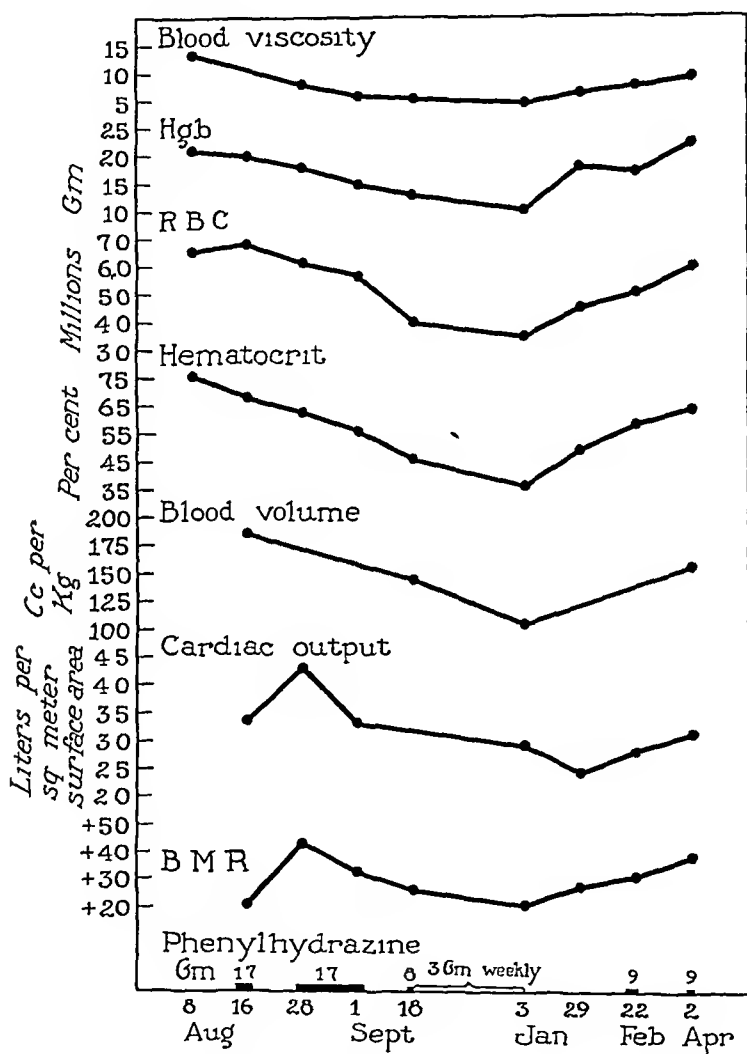
The patient returned on Jan 2, 1934, for examination, occasional tinnitus and palpitation being her only complaints. She had gained 30 pounds (13.6 Kg). Discoloration of the skin and mucous membrane was much less marked. The

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4 Grollman, Arthur. Solubility of Gases in Blood and Blood Fluids, *J Biol Chem* 82 317-325 (May) 1929

heart was slightly enlarged, and a systolic murmur was audible over the entire precordium. The spleen and liver were enlarged. After a number of laboratory tests were made the patient was dismissed on January 4. The same day she fell on the ice, fracturing the neck of the left femur. During her long stay in the hospital as a result of this mishap, further investigations were carried out.

The laboratory findings during the time the patient was under observation are given in the accompanying figure. At the time of her first admission to the hospital she had a high total blood volume, 185 cc per kilogram of body weight, with a plasma volume of 59 cc per kilogram. The viscosity of the blood was



The cardiac output and the hematologic values in polycythemia vera (case 1)

increased to 136, the value for hemoglobin was 21.3 Gm per hundred cubic centimeters, and the erythrocytes numbered 6,700,000 per cubic millimeter. The hematocrit reading was 73 for the percentage of cells. All these abnormally high values were reduced under treatment and remained nearly normal or slightly subnormal until March (no phenylhydrazine had been given for one month), when they began to rise rapidly. The leukocyte count was persistently elevated, and it increased during the intensive administration of phenylhydrazine. The differential count revealed neutrophilia and the presence of an occasional myelocyte. The values for blood urea, uric acid, sugar, calcium, phosphorus,

chlorides and serum proteins were normal. The albumin-globulin ratio was 17:1. The urine consistently contained albumin and erythrocytes. The number of blood platelets and the coagulation and bleeding time were normal. An electrocardiogram disclosed left ventricular preponderance, with an inverted T wave in lead III and some nodal premature contractions. The basal metabolic rate was elevated, a finding not uncommon in cases of polycythaemia vera, the cause of which is unknown. Table 1 gives the detailed findings throughout the period of observation on the cardiac output and basal metabolism, whereas the figure shows the relationship of these factors to the condition of the blood. According to Grollman, the cardiac output of a normal subject under strictly basal conditions is remarkably constant and is proportional to the area of body surface. Under strictly basal conditions a normal adult has a cardiac output of  $22 \pm 0.3$  liters per minute per square meter of body surface.

The cardiac output of this patient at the beginning of treatment was considerably above normal, 3.37 liters per minute per square meter of body surface, and on one occasion it rose to 4.3 liters (table 1). At this time the basal metabolic rate was +43 per cent. On September 1 the cardiac output per square

TABLE 1—*Cardiac Output in a Case of Polycythaemia Vera (Case 1)*

Date	Surface Area, Sq Meters	Blood Pressure	Pulse Rate	Oxygen Consumption, Cc per Sq Meter per Minute	Basal Metabolic Rate	Cardiac Output, Liters per Minute per Sq Meter of Surface Area	Systolic Output, Cc
8/16/33	1.32	100/62	68	148	+21	3.55 3.20	53 48.5
8/28/33	1.33	120/64	89	174	+43	4.30	65
9/1/33	1.34	108/70	90	160	+33	3.30	49
1/3/34	1.47	100/64	70	149	+21	2.9	61
1/29/34	1.47	114/74	80	154	+27	2.4	43
2/22/34	1.47	106/72	87	154	+31	2.8	47
4/2/34	1.48	114/88	94	165	+38	3.1	48

meter was 3.3 liters per minute, and the basal metabolic rate was +33 per cent. The viscosity of the blood and the value for hemoglobin were practically normal, and the erythrocyte count and the percentage of cells as determined with the hematocrit were only slightly elevated (figure). The volume of blood on September 18 was somewhat reduced but was still considerably above normal. When the patient returned on Jan. 2, 1934, the volume of blood had dropped almost to normal, other findings revealed slight anemia. The basal metabolic rate was still elevated, +21 per cent, but the cardiac output was now 2.9, which, while not normal, showed an approach toward that figure. On January 29 the cardiac output was 2.4 liters per minute per square meter, within the normal range, and the basal metabolic rate was +27 per cent, on February 22 the output was 2.8 liters and the basal metabolic rate +31 per cent. On April 2 the cardiac output had risen to 3.1 liters and the basal metabolic rate to +38 per cent. The volume of the blood, number of erythrocytes, the value for hemoglobin and the percentage of cells as determined with the hematocrit also had increased at this time.

While the elevation of the metabolic rate in this case may partially account for the increased cardiac output, it could not have been the

entire cause. Perusal of the foregoing data shows that in the individual determinations the cardiac output did not always vary directly with the basal metabolic rate, although both curves follow the same general trend. The cardiac output was increased more than the oxygen consumption at the beginning of treatment, as the arteriovenous oxygen difference was below normal. The increased cardiac output cannot therefore be attributed only to the increased tissue metabolism. Similar findings were cited by Grollman in cases of hypertension in which there was an elevated basal metabolic rate and also in cases of hyperthyroidism by Boothby and Rynearson.<sup>5</sup> The last-named investigators showed that the cardiac output of patients with exophthalmic goiter was increased above the values produced in normal subjects by work that caused a similar increase in the consumption of oxygen. In the present case the cardiac output was increased above the normal curve produced by work to about the same extent as in cases of hyperthyroidism.

One can only theorize in regard to the cause of the additional elevation of the cardiac output in this case of polycythaemia vera. Considering only the factor of the increased concentration of hemoglobin in the blood, a decreased cardiac output might be expected. In cases of anemia in which the concentration of hemoglobin fell below 50 per cent, Dautrebande found an increased cardiac output. In studying the cardiac output at high altitudes Grollman found an initial increase when the subject ascended to a high level, with a gradual reduction in the cardiac output as the amount of hemoglobin in the blood increased. In polycythemia an increased percentage of hemoglobin is associated with a markedly increased total volume of blood, an increased number of erythrocytes per unit of blood, an increased viscosity of the blood and consequently a decreased amount of serum. Any of these three factors might influence the volume of the blood put out by the heart per minute. Ingestion of fluid has been found to cause a rise in the cardiac output, which conceivably is due to the sudden dilution of the blood, with a decreased carrying capacity for both oxygen and carbon dioxide of a unit volume of blood, or to an increase in the blood volume. Locke's solution increases the output more than does the ingestion of water, probably from the latter cause. Gregg and Wiggers<sup>6</sup> have stated that the expected hemodynamic effects in polycythemic hypervolemia would be similar to those produced through an increased venous return plus greater viscosity of the blood, namely, a rise in the venous pressure,

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5 Boothby, W. M., and Rynearson, E. H. Increase in Circulation Rate Produced by Exophthalmic Goiter, Compared with That Produced in Normal Subjects by Work, *Arch Int Med* **55** 547-557 (April) 1935.

6 Gregg, D. E., and Wiggers, C. J. The Circulatory Effects of Acute Experimental Hypervolemia, *Am J Physiol* **104** 423-432 (May) 1933.

an increase in the diastolic size of the ventricles and an augmented systolic discharge with a rise in the arterial pressure. In acute experimental hypervolemia in dogs they found an increased return of blood to the heart, with an increased systolic discharge from the left ventricle.

The increase in the number of erythrocytes in polycythemia is necessarily associated with a decrease in the plasma volume per unit of blood. Most of the nutrients to the tissue, aside from oxygen, are carried in the plasma. If insufficient plasma is present to act as a solvent for these substances from the gastro-intestinal tract, it is possible that an increased demand by the tissues for more nutrient material could be a factor in bringing about an increased cardiac output.

In this case of polycythemia when the blood volume and hematocrit readings were elevated the cardiac output was increased. When these values had returned practically to normal the cardiac output was lowered and the arteriovenous oxygen difference was more nearly normal, the cardiac output tending, on the average, to vary with the amount of oxygen consumed. As the blood volume and hematocrit readings rose again, the cardiac output became elevated. It is possible that the increased volume of blood could influence the output of the heart and also that the increased viscosity could play a part. Another factor could be the increased demand of the tissue for nutrients, due to a decreased amount of serum per unit of blood, thus causing an increased output per minute. There is another question which is important in the determination of the cardiac output by a gas method in cases of polycythemia, and that is the difference in solubility of acetylene in polycythemic and in normal blood. Grollman found a slight difference in the solubility of this gas in the blood serum and in the corpuscles of the dog. In one case of polycythemia the solubility of acetylene was 0.71 cc of the gas in 1 cc of blood, as compared with 0.74 cc of the gas in 1 cc of normal blood, this difference, however, does not seem great enough to affect measurably the calculated cardiac output.

CASES 2, 3 and 4—Determinations of the cardiac output and detailed studies of the blood have been carried out in three other cases of polycythemia vera (table 2). In case 2 there was a normal cardiac output, and the basal metabolic rate was within normal limits. The volume of blood, the viscosity and other values were considerably elevated. In case 3 the cardiac output was essentially within normal limits, although there was a definite drop in the output as the volume of blood, the viscosity and the hematocrit reading returned toward normal. At the time of the third determination this patient had anemia, which might have accounted for the fact that the cardiac output was again increased. In case 4 there was a slight elevation of the cardiac output, with a normal basal metabolic rate, the cardiac output dropping as the blood volume, the hematocrit reading, the hemoglobin content and the erythrocyte count returned to normal.

None of these three patients showed a marked deviation from the normal in the cardiac output. In cases 3 and 4, however, there was a suggestion of correlation between the cardiac output and the hematologic status, all the values decreasing at the same time. The largest volume of blood and also the largest cardiac output were noted in case 4. None of these patients exhibited the marked elevation of blood volume which was present in case 1. It may be that the volume of blood must be greatly elevated to augment the cardiac output. Further determinations correlating the changes in the blood and in the cardiac output are necessary to warrant a definite conclusion.

TABLE 2—*Cardiac Output, Metabolic Rate and Hematologic Values in Polycythaemia Vera*

Case	Date	Cardiac Output, Liters per Minute per Sq Meter of Surface Area	Basal Metabolic Rate	Blood Volume Cc of Whole Blood per Kg of Body Weight	Blood Viscosity	Hematocrit Reading, Percentage	Hemoglobin, Percentage	Erythrocytes, Millions
2		2.18	—2	137.0	13.0	73.0	20.9	6.50
3	5/18/34	2.49	+9	131.0	11.6	69.5	21.2	8.45
	5/29/34	2.02	+5	88.4	5.6	37.7	12.3	4.96
	6/ 4/34	2.60	+1			30.0	10.6	2.69
4	5/29/35	3.00	+7	188.0	10.0	67.8	22.3	6.47
	6/ 6/35	2.80	+6					
	6/30/35	2.46	—2	95.0		46.0	14.8	4.73

#### SUMMARY

Determinations of the cardiac output and detailed studies of the blood have been carried out over a period of eight months in a case of polycythaemia vera. The cardiac output, which was elevated considerably above normal prior to the institution of treatment, decreased as certain hematologic values approached normal. The increase in the basal metabolic rate in this case does not entirely explain the increased cardiac output. It is suggested that the increased volume of blood may be a factor in this regard. Another factor may be the decreased percentage of plasma per unit of blood, causing a deficiency in the transportation of nutrient substances to the tissue. The cardiac output in three additional cases of polycythaemia vera is reported, in two the findings were within normal limits, and in one there was a slight elevation of the output. Two of these patients were followed during treatment, and it was observed that the cardiac output tended to decrease as the blood picture approached normal.

# MONOCYTIC LEUKEMIA

## REPORT OF EIGHT CASES

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NEW HAVEN, CONN

In 1913 Reschad and Schilling-Torgau<sup>1</sup> reported the first case of monocytic leukemia. Two years later the second case was described by Fleischmann<sup>2</sup>. In 1930 Dameshek<sup>3</sup> reviewed the literature and found only ten acceptable case reports. Clough<sup>4</sup> in 1932 brought the number up to twenty-three.

On a subsequent examination of the literature a total of seventy-seven reports of well established cases were found. Of these four had not been available to previous reviewers, and seventy-three have appeared since Clough's report. The addition of eight cases which have come under our observation and which are herein presented brings the total number of acceptable cases described to eighty-five. In addition to these, approximately twenty-five case reports have been rejected because of insufficient or unconvincing data.

Monocytic leukemia has always been regarded as an exceedingly rare disease. However, the many case reports which have been published since interest in the condition has been aroused and the appearance of eight cases in New Haven in a period of three years suggest that it is considerably more prevalent than was previously supposed. From January 1933 to January 1936 forty-eight cases of leukemia were recorded in the New Haven and Grace hospitals and were distributed as follows:

	Myelogenous	Lymphatic	Monocytic	Unclassified
Acute	6 (13%)	9 (19%)	8 (17%)	1
Chronic	12 (35%)	12 (25%)		

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From the Department of Internal Medicine, Yale University School of Medicine, and the Medical Service of the New Haven Hospital and Grace Hospital.

1 Reschad, H., and Schilling-Torgau, V. Ueber eine neue Leukämie durch echte Uebergangsformen (Splenozystenleukämie) und ihre Bedeutung für die Selbstständigkeit dieser Zellen, München med Wchnschr **60** 1981 (Sept 9) 1913

2 Fleischmann, P. Der zweite Fall von Monozytenleukämie, Folia haemat **20** 19 (Oct 1) 1915

3 Dameshek, W. Acute Monocytic (Histiocytic) Leukemia, Arch Int Med **46** 718 (Oct ) 1930

4 Clough, P. W. Monocytic Leukemia, Bull Johns Hopkins Hosp **51** 148 (Sept ) 1932

Levine<sup>5</sup> reported that of six thousand and sixty-six autopsies performed at the Cook County and Grant hospitals, of Chicago, between 1931 and 1934, there were fifty-eight in cases of leukemia, of which thirty-six were cases of acute leukemia. Six of these were cases of monocytic leukemia which constituted 10.3 per cent of all the cases of leukemia and 16.7 per cent of the cases of acute leukemia. Doan and Wiseman<sup>6</sup> reported that of seventy-six cases of leukemia studied from 1930 to 1934, 12 (or 16 per cent) were instances of the monocytic type. If the incidence of monocytic leukemia ranges between 10 and 17 per cent of all cases of leukemia, as these figures suggest, it is evident that in general many cases are being overlooked.

#### REPORT OF CASES

CASE 1—J. J., a 65 year old married, unemployed Negro (formerly a coal heaver), entered the New Haven Hospital because of sore throat and bleeding gums of four weeks' duration. As a child he had whooping cough and measles. Gonorrhea developed when he was 18. When he was a young man he is said to have had syphilis and to have received injection treatments until the Wassermann reaction became negative. Eight years before his admission to the hospital he suffered from attacks of asthma, which responded to treatment. Ten months before his admission to the hospital he was treated for a chronic ulcer of the anterior surface of the right leg, which healed after treatment with local applications. At that time it was recorded that his diet was inadequate in foods containing protein and vitamins. There was no lymphadenopathy and the liver and spleen were not enlarged.

Four weeks before his admission to the hospital increasing soreness of the throat, mouth, tongue and gums began, with slight intermittent bleeding from these mucous membranes. Two weeks later enlargement of the cervical lymph nodes and swelling of the ankles were noted. There had been a loss of 10 pounds (5 Kg.). Dietary deficiency was evident. His family of four adults had been subsisting on \$4 a week.

*Physical Examination*—The patient was undernourished, pale, weak and obviously seriously ill. Dyspnea on slight exertion was evident. There were numerous isolated purpuric spots on the skin. The gums were boggy and bled easily. The tonsils were enlarged, they were a peculiar gray and bore small patches of greenish gray exudate. There were hemorrhagic spots on the mucous membranes of the mouth and tonsils. Sclerotic changes of the vessels of the fundus oculi were present, and hemorrhagic spots and a few small scars were seen. The lymph nodes of the cervical, occipital, axillary, inguinal and epitrochlear regions were moderately enlarged but not tender. The heart was slightly hypertrophied, and a systolic murmur was heard over the entire precordium. There was pronounced sclerosis of the arteries accessible to palpation. Abdominal and neurologic examinations revealed no abnormality.

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5 Levine, V. Monocytic Leukemia, *Folia haemat* 52 305 (Sept) 1934

6 Doan, C. A., and Wiseman, B. K. The Monocyte, Monocytosis and Monocytic Leukosis. A Clinical and Pathological Study, *Ann Int Med* 8 383 (Oct) 1934



*Laboratory Examination*—The patient's blood was in group 1, according to the classification of Jansky. The Kahn test for syphilis was negative. Blood cultures were sterile. There were 150,000 platelets per cubic millimeter of blood, according to the method of Rees and Ecker. The bleeding time was eight minutes. The clotting time was two minutes and forty-five seconds by the capillary method and three minutes and thirty seconds by the test tube method. The number of erythrocytes decreased from 2,100,000 per cubic millimeter at the time of the patient's admission to the hospital to 1,500,000 before his death, and the hemoglobin value declined from 40 per cent (61 Gm) to 30 per cent (46 Gm). The leukocyte count, on the other hand, increased rapidly from 61,000 to 179,000 per cubic millimeter. The cells of the monocytic series constituted from 89 to 96 per cent of the leukocytes. Ninety-five per cent of the leukocytes contained oxidase. The erythrocytes were hypochromic, an occasional normoblast was seen and moderate anisocytosis and poikilocytosis were noted. No sickle cells were seen.

The predominating leukocytes varied markedly in size, some were unusually large, but the majority ranged between 10 and 15 microns in diameter. The nuclei were round, oval or indented, the adult horseshoe shape being practically absent. In a number of instances the nuclei were grossly irregular or lobed. The diffuse homogeneous network of chromatin was typical of the monocyte, and its color varied with the intensity of the stain from grayish blue to purple. Occasional nucleoli were seen. The nuclear outline was unusually indistinct. The cytoplasm was scant in most cells and abundant in a few. It had a hazy, pale blue, ground glass appearance, with vacuoles in some of the cells. The majority of the cells contained no visible granules, in only a few were small lilac granules seen. The outline of the cells was usually irregular, scalloped or interrupted by budlike projections or actual pseudopodia. No clasmotocytes (Sabin) were seen.

Supravital studies showed that the predominant leukocytes were from 10 to 15 microns in diameter and were ordinarily motile. This activity consisted of a slow change in form, with actual progression seen in some instances. The nuclei were more often horseshoe shaped, bean shaped and irregular than was apparent in fixed smears. Practically all the leukocytes contained salmon-red, neutral red vacuoles grouped in clusters, which in the less actively motile cells assumed the characteristic rosette arrangement. Peripheral to the neutral red vacuoles, mitochondria in varying numbers were scattered throughout the cytoplasm.

The phagocytic activity of the leukocytes was studied with trypan blue. When this dye was added to the blood *in vitro*, 75 per cent of the leukocytes took it up. Thirty cubic centimeters of a 5 per cent solution of the dye was injected intravenously. Samples of blood drawn after five, ten and twenty minutes were studied, and it was found that in the first sample a few cells contained trypan blue granules, whereas in subsequent samples there were granules in 50 and 94 per cent of the leukocytes, respectively.

The urine was normal except for occasional hyaline and granular casts. The feces contained varying amounts of occult blood, detected by the guaiac test, and mucus in small amounts. Roentgenographic examination of the wrists, hands, tibiae and fibulae were negative. Biopsy of an inguinal lymph node was performed, and a description will be given subsequently.

*Clinical Course*—The temperature varied between 99.4 and 103.5 F, with daily swings to both extremes. The patient rapidly grew worse, and ulceration of the tonsils and gums increased progressively. No specific therapy other than small

doses of potassium arsenite was attempted. Death occurred twelve days after the patient's admission to the hospital. The total duration of the disease was approximately forty days.

*Necropsy*—The anterior cervical, posterior cervical, submental, submaxillary, supraclavicular, axillary, inguinal and mesenteric lymph nodes were enlarged, the largest measuring 2.5 cm in length. The hilar and mediastinal lymph nodes were not hypertrophied. On microscopic examination the normal architecture of an inguinal lymph node removed during life was seen to have been entirely replaced by large mononuclear cells resembling those seen in germinal centers. They contained large, round or oval, vesicular nuclei which varied considerably in size, shape and staining intensity. They had scanty rims of pink-staining cytoplasm, and these cells were frequently seen in a state of mitotic division. The capsule and adipose tissue at the hilus were invaded by these cells.

No thymic tissue was recognized.

The spleen weighed 495 Gm. The splenic pulp bulged slightly from the capsule on the cut surface, but it was dry and red-brown. The malpighian bodies could not be distinguished. Microscopically the picture was similar to that of the lymph nodes. The follicles could barely be recognized. Staining indicated an increased amount of reticulum.

The liver weighed 2,350 Gm. On section the lobular markings were distinct, and the red-brown surface was spotted with minute gray dots, concentrated in the periportal regions. Microscopically, the hepatic sinusoids were dilated, and the hepatic cords were atrophied. In many places, particularly in the periportal spaces, the compression of tissue by the mononuclear cells was so marked that large islands of these cells were formed. Most of the cells were round and had large, round, pale nuclei and little cytoplasm. Some were foamy and had large amounts of cytoplasm and small nuclei. Others were small and had small hyperchromatic nuclei, which were round, irregular or lobulated. These cells did not resemble polymorphonuclear leukocytes. In places groups of basophilic cells were seen. In the sinusoids Kupffer cells appeared in various stages of morphologic change. Occasionally some rounded ones were seen lying free in the lumens. Others were partially attached to the walls of the sinusoids.

The bone marrow of the sternum and vertebral bodies was red and cellular. The normal marrow was replaced by the typical mononuclear cells. Many of these appeared to be attached to the reticular network. The absence of granulocytes was evident with both Wright and Giemsa stains. A photomicrograph of the bone marrow from a vertebra is presented in figure 1A.

There was extensive infiltration of the heart, aorta, lungs, stomach, intestines, pancreas, adrenal glands, kidneys, prostate, testes, tonsils, thyroid gland and skin with typical mononuclear cells. There were scattered petechial hemorrhages in varying degree into these organs.

CASE 2—C. B., a 23 year old dentist's assistant, white, American, unmarried, entered the New Haven Hospital complaining of weakness and metrorrhagia. Except for chickenpox, measles, mumps, a tonsillectomy at 7 years of age and an appendectomy at 11 years, the patient's general health had been good until the present illness. Five and a half months before her admission to the hospital a generalized rash of purpuric spots developed. Subsequently similar spots appeared in smaller numbers. With the onset of purpura the patient first noted headache in the occipital region, backache and urinary frequency, which was ascribed by her physician to pus in the urine. At the same time leukocytosis was discovered. Despite the administration of solution of potassium arsenite, the weakness and

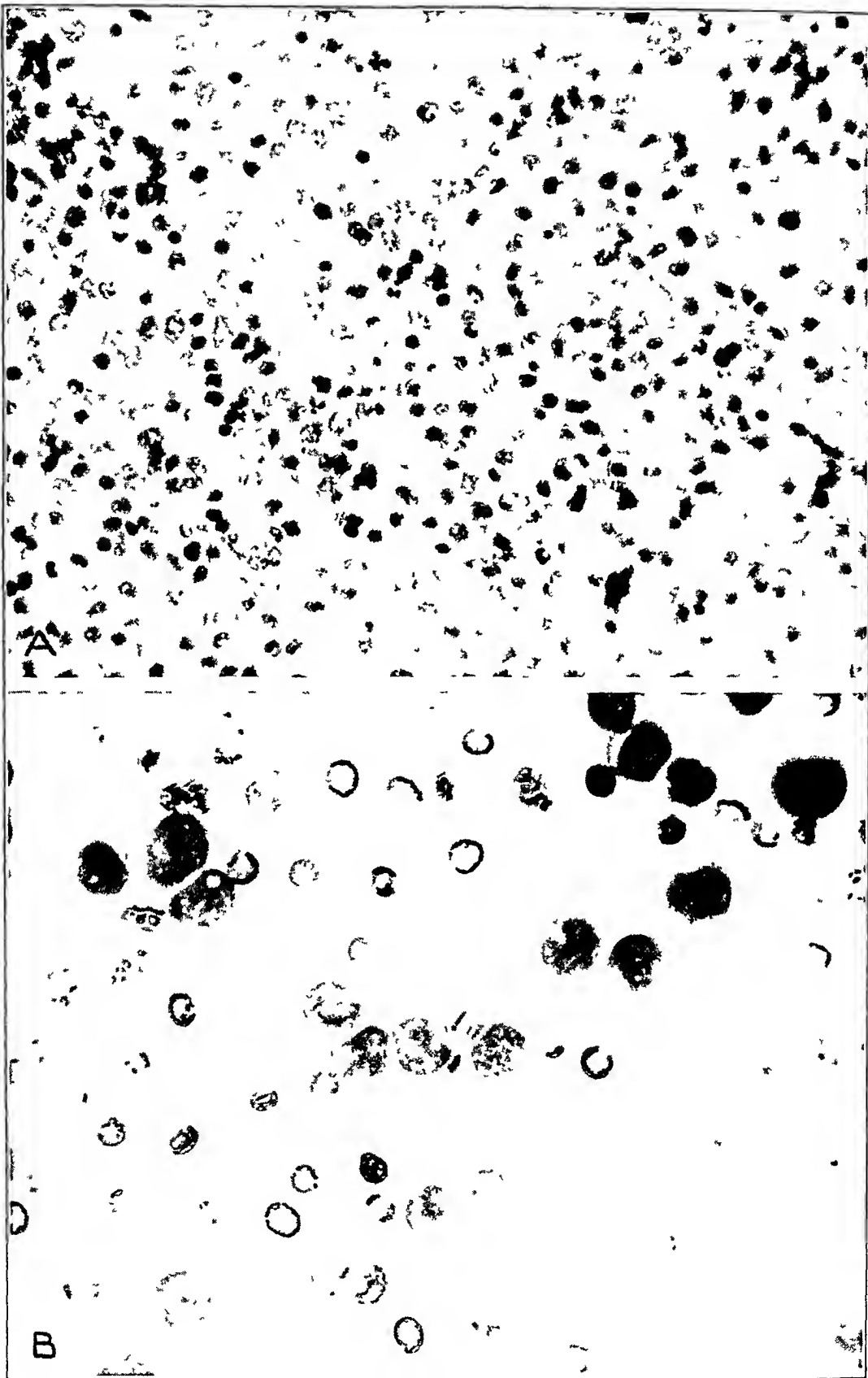


Fig 1—*A* (case 1), photomicrograph of bone marrow from a vertebra,  $\times 500$ . The normal cells of the marrow have been replaced by a dense infiltration of typical mononuclear cells. Normoblasts and other young cells of the erythrocytic series are visible, but cells of the myelogenous series are rarely seen. *B* (case 2), photomicrograph of the blood,  $\times 500$ . These leukocytes belong to the monocytic series. Note the variation in the size of the cells and the shapes of the nuclei. Evidences of pseudopodial activity are present, and in some of the cells nucleoli are visible. The dark shadows in the erythrocytes are a staining artefact.

palpitation became steadily worse. Menorrhagia with the passage of clots commenced two weeks before and persisted until her admission to the hospital. Blurring of vision set in one week prior to her admission to the hospital and on the day of admission nosebleeds began.

*Physical Examination*—The patient was pale, slightly emaciated and obviously critically ill. Scattered over the body were isolated purpuric spots and ecchymotic areas. There was a patchy brown discoloration of the neck and abdomen, which may have been due to previous arsenic therapy. The Rumpel-Leede capillary resistance test was strongly positive after five minutes. There were dry clots of blood in the nares. Numerous hemorrhagic spots, some with distinct white centers, were seen in the fundi. The retinal venules were distended and tortuous, and the nerve borders were indistinct. There were dry, crusted, ulcerative lesions at the angles of the mouth. The oral mucous membranes were boggy, and desquamation was easily produced by wiping. The tonsils were swollen and edematous and had the appearance that is occasionally seen preceding ulceration. Generalized lymphadenopathy was present, but the nodes were only moderately enlarged. There was a systolic murmur audible over the entire precordium. The lower border of the spleen was felt 4 fingerbreadths and the edge of the liver 2 fingerbreadths below the costal margin.

*Laboratory Examinations*—There were 770,000 red blood cells and 46,250 leukocytes per cubic millimeter. The hemoglobin value was 15 per cent, of 15.4 Gm. A differential count showed 1 per cent neutrophils, 6 per cent lymphocytes, 31 per cent monocytes and 62 per cent "blasts," probably monoblasts. Fluctuations in the number of leukocytes are charted in figure 2. Cells identified as clasmatocytes (Sabin) were present in proportions varying from 1 to 14 per cent of the total number of leukocytes. The clasmatocytes were the largest cells seen in the fixed and supravital preparations. Fixed with Leishman's stain, they were seen to vary from 18 to 30 microns in diameter. The nuclei were constantly reniform or horseshoe shaped. The granules, which were ordinarily not numerous, were arranged about the nucleus, usually in the *Hof*. A photomicrograph of a smear is presented in figure 1B.

Supravital examinations and differential counts by this technic were made at repeated intervals during the course of the illness. The appearance, motility and behavior toward neutral red and janus green of the monocytic elements was similar to that described in previous cases.<sup>7</sup> The clasmatocytes were identified by their greater size, their horseshoe or reniform nuclei and the irregular distribution of the neutral red vacuoles the hue of which was more variable than that of the monocytes. No distinction in regard to motility could be made. Particles of janus green were not evident in the clasmatocytes. After several blood transfusions phagocytosed, crenated red blood cells were commonly seen in both clasmatocytes and monocytes.

As indicated in figure 2, there was a gradual fall in the total number of leukocytes. This was accompanied with a complete disappearance of cells of the granulocytic series and a gradual drop in the actual and relative numbers of monocytic elements. The number of cells of the lymphocytic series fluctuated only slightly throughout the course of the illness.

Hemolysis appeared in a 0.44 per cent saline solution and was complete in a 0.34 per cent solution. The limits in a normal control were 0.44 per cent and 0.36 per cent, respectively. The patient's blood was in group 1, according to the classification of Jansky. The bleeding time was two minutes and forty seconds.

<sup>7</sup> Dameshek<sup>3</sup> Clough<sup>4</sup>

The clotting time by the capillary tube method likewise was two minutes and forty seconds. There were from 30,000 to 150,000 platelets per cubic millimeter of blood. From 20 to 30 per cent of the leukocytes contained granules that showed a positive reaction to the Goodpasture peroxidase stain.

The Kahn test was negative. The heterophile antibody agglutination test was negative. Blood cultures were sterile until shortly before the patient's death, when *Bacillus coli* was obtained. Staphylococci, *Micrococcus catarrhalis*, a hemolytic strain of *Staphylococcus albus* and hemolytic streptococci were obtained from cultures of sputum.

Except for small amounts of albumin, the urine was normal. There was no Bence-Jones protein in the urine. The feces were normal.

*Clinical Course*—The temperature was continually high, ranging between 101 and 105.5 F. The pulse rate fluctuated between 105 and 160. Despite eight blood

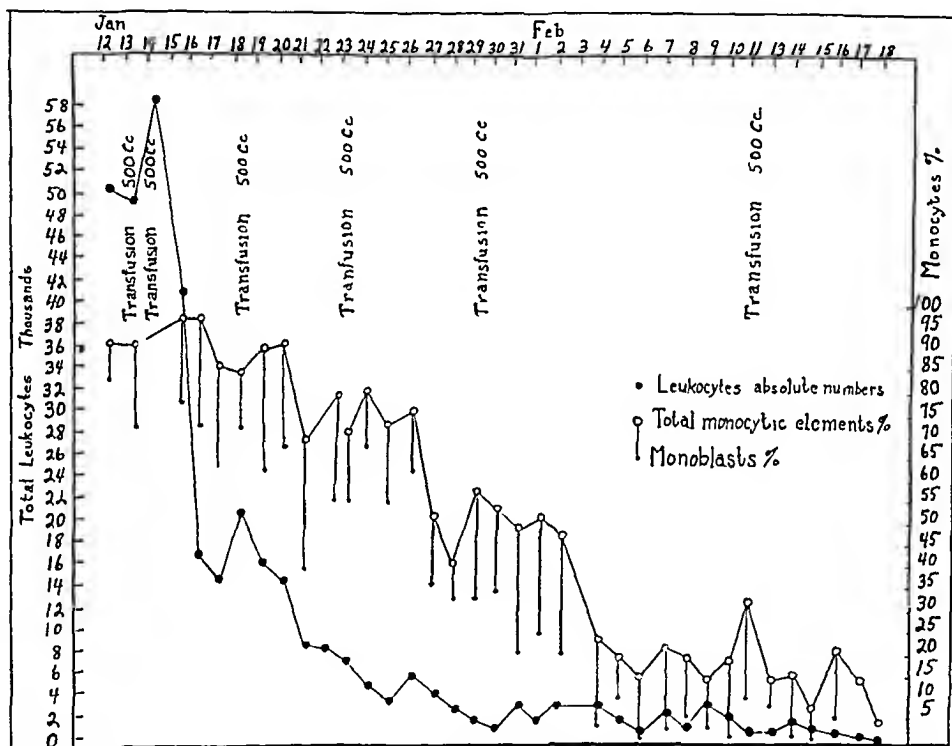


Fig 2 (case 2) —Fluctuations in the number and percentage of leukocytes in a case of monocytic leukemia. Note the terminal leukopenia.

transfusions, the patient's condition steadily grew worse. Shortly after her admission to the hospital deafness and signs of bilateral acute otitis media developed. A cough productive of blood-tinged sputum and signs of bronchopneumonia appeared. The lesions at the angles of the mouth developed slowly into deep, necrotic ulcers with a dirty, grayish yellow base and only slight surrounding inflammation. Similar necrotic ulcers developed in the soft palate and anus. Cultures of material from these lesions contained a heterogeneous growth of organisms, which included spirilla and fusiform bacilli. On the thirty-seventh day of hospitalization the patient died. The total duration of the illness was approximately seven months.

*Necropsy*—There were scattered petechial hemorrhages into most of the tissues and serous surfaces.

There was generalized enlargement of the lymph nodes. On section they were deep red-brown. The general architecture of the lymph nodes was moderately well preserved. The striking picture seen in all the nodes was that of infiltration with large numbers of mononuclear phagocytic cells containing red blood cells and blood pigment. The sinusoids and capillaries were distended with these cells, and the surrounding loose fatty tissue likewise was invaded. There was a definite increase in the amount of fibrous connective tissue.

The spleen weighed 345 Gm. The surface was deep red on section, and malpighian bodies and trabeculae were discernible. There was a diffuse infiltration of large mononuclear phagocytic cells containing golden brown pigment and red blood cells. Small amounts of pigment lay free in the tissue spaces. The malpighian bodies were for the most part small. There appeared to be a diffuse increase in the amount of reticular connective tissue.

The liver weighed 1,785 Gm. The cut surface was light brown, mottled with yellow and red, and the lobulations were readily seen. For the most part the hepatic cords were well preserved, in some zones the cells were vacuolated. The veins and sinusoids were distended with large mononuclear cells. In some of the portal zones the connective tissue appeared loose and edematous, and there was a slight increase in the amount of fibrous connective tissue. Figure 3A is a photomicrograph of a section of the liver.

The tibial marrow was relatively aplastic. There was much fat, and the venous channels were widely dilated with blood. The marrow from the sternum showed a striking absence of myeloid elements. Whether or not young myelocytes and myeloblasts were present could not be determined. Mononuclear cells, probably monocytes, were present. Cells of erythroblastic series, notably erythroblasts and normoblasts, were present in small numbers. The absence of myeloid cells was in keeping with the clinical picture of a continuously decreasing leukocyte count, which fell finally to less than 1,000 cells per cubic millimeter.

In a preparation from the rectum was noted a loss of the normal mucosa, and the tissue in this region was necrotic, opaque and amorphous. Below this zone the tissue was infiltrated by mononuclear cells, round cells, plasma cells and polymorphonuclear cells, and fibroblastic proliferation was evident.

There was organizing and necrotizing focal pneumonia of the lungs. In some areas large phagocytic cells with vesicular nuclei and abundant cytoplasm, containing red and white blood cells, were conspicuous.

There was hemorrhage into the left middle ear and a thin, yellow exudate was present in the region of the middle ear both on the left and on the right.

No cellular infiltration of the heart, pancreas, adrenal glands, kidneys or thyroid gland was evident.

CASE 3—H. G., a 12 year old white American schoolboy, was admitted to the New Haven Hospital because of fever. The child was born at full term, weighing  $7\frac{1}{2}$  pounds (3,400 Gm.), and the delivery was normal. He had measles, mumps, whooping cough, chickenpox and at 12 months a convulsion the cause of which was not determined. He had been vaccinated for smallpox. The Schick test was negative.

Three weeks before his admission to the hospital a slight loss of appetite, constipation, drowsiness and pallor were first noticed. He complained of weakness and a dull constant pain in the right upper quadrant of the abdomen. Two weeks before his admission to the hospital a pain, interpreted as a toothache, developed on both sides of the lower jaw. Because of this a tooth was extracted on the day before his admission to the hospital.

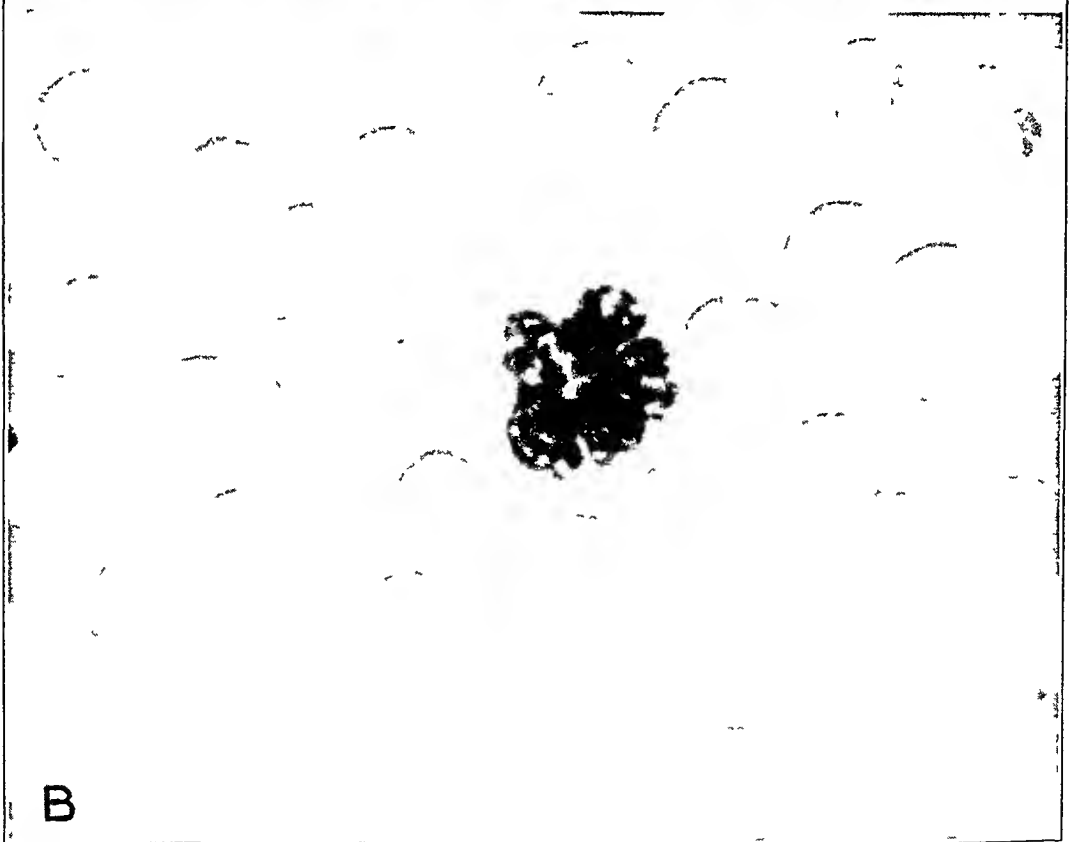
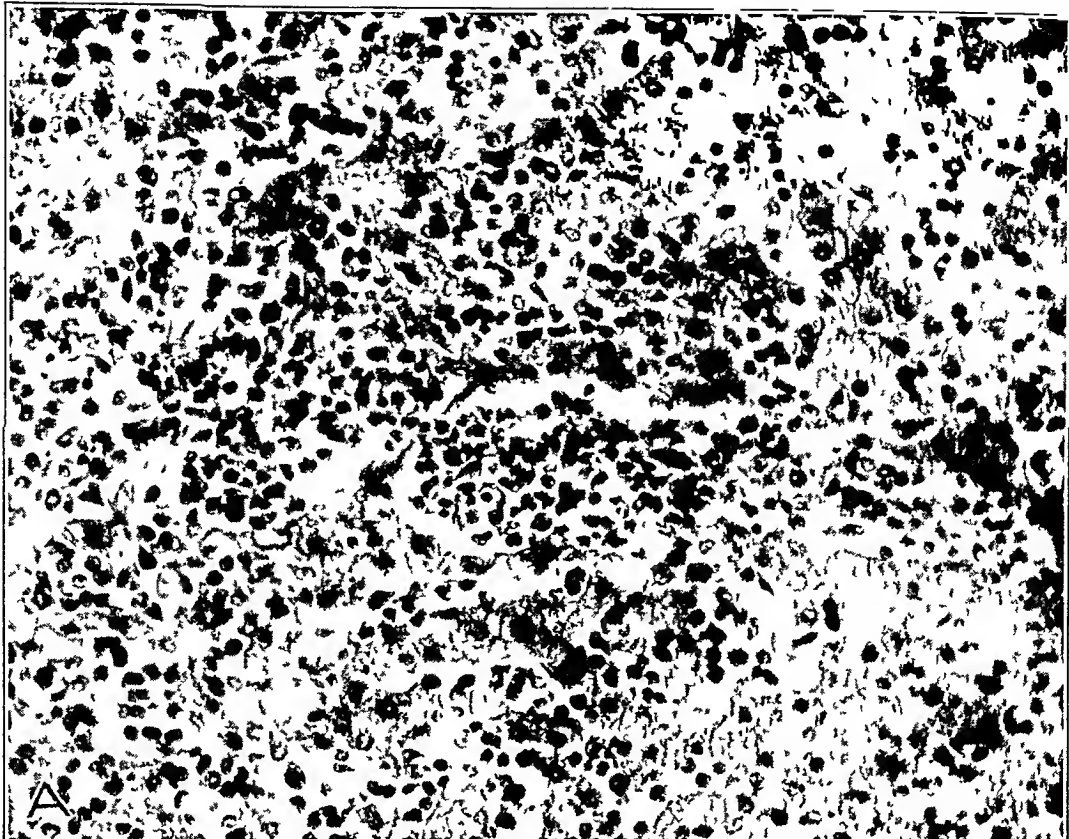


Fig 3—*A* (case 2), photomicrograph of a section of the liver,  $\times 250$ . Note the massive infiltration with mononuclear cells, causing atrophy and destruction of the hepatic cords and an increase in the amount of connective tissue. *B* (case 7), photomicrograph of an unusual leukocyte from a patient with monocytic leukemia,  $\times 1,125$ . Note the segmentation of the nucleus into a radial grapelike cluster of densely stained lobes. The cytoplasm is delicately stained and contains no granules. A large vacuole is discernible, and the irregular scalloped outline of the cell can be detected.

*Physical Examination*—The boy was pale and looked sick. There were a few petechiae in the skin. The gums were swollen, red and tender. There were hemorrhagic spots on the tongue and soft palate. The breath had a foul odor. The tonsils were injected and extraordinarily large. There was slight generalized lymphadenopathy, but only the cervical lymph nodes were markedly enlarged, those at the angles of the jaw were approximately 4 cm in the long diameter. Examination of the eyes revealed globular and flame-shaped subhyaloid and preretinal hemorrhages in the fundi. There was a systolic murmur best heard at the base of the heart. There was diffuse tenderness on palpation of the abdomen. The edge of the spleen was felt 3 fingerbreadths and the liver 2 fingerbreadths below the costal margin.

*Laboratory Examination*—The hematologic data are given in table 1. The cells of the monocytic series ranged from fully mature specimens with horseshoe-shaped nuclei to young monoblasts containing one or more nucleoli. The borders of the adult cells were frequently irregular in outline and sometimes scalloped, occasionally actual pseudopodia were seen. The essential characteristics of the cells conformed precisely with those previously described.

TABLE 1—Data on the Blood in Case 3

Date	Erythrocytes, Thousands	Hemoglobin, %	Leukocytes	Differential Count, Leishman Stain			
				Neutrophils, %	Lymphocytes, %	"Blasts," %	Monocytes and Monoblasts, %
7/29	1,900	40	6,100				
7/30	2,600	46	13,700				
7/31	2,200	47	12,500	10	10	1	79
8/ 1	2,200	44	28,000	5	7	2	86
8/ 2	1,900	42	23,500	1	25		74
8/ 3	1,900	40	40,600		15		85
8/ 4	1,700	40	67,000	2	25		73
8/ 5	900	30	78,800	2	22		75
8/ 6	1,800	40	75,200	4	10		86

There were slight poikilocytosis and anisocytosis and occasional stippling of the red blood cells. The reticulocyte count varied from 3 to 0.2 per cent. From 390,000 to 410,000 platelets per cubic millimeter of blood were present. The bleeding time increased from three minutes on August 3 to ten minutes on August 5. The clotting time remained between two and four minutes. The heterophile antibody agglutination test was negative. The Kahn test was negative. The blood was in group 2, according to the Jansky classification. Blood culture was sterile.

The reaction to the tuberculin test was negative in all dilutions. The Schick test showed a positive reaction. Culture of material from the nose contained staphylococci and diphtheroids, and the usual flora, including hemolytic streptococci, were grown from material from the throat. There were occasional waxy casts, many large granular casts and albumin in the urine (1 plus).

The spinal fluid contained 7 leukocytes and 165 red blood cells per cubic millimeter. Stereoroentgenographic examination of the chest revealed unusually prominent hilar regions, probably owing to enlarged paratracheal nodes, and there was also an increase in the coarseness of the markings throughout both pulmonary fields.

*Clinical Course*—There were daily fluctuations of temperature within the limits of 100.5 and 105 F. The lymph nodes, liver and spleen rapidly increased in size, the spleen finally extending below the level of the umbilicus. Ulceration of



the gums developed and spread to the lower lip and the anterior faucial pillars. These mucous membranes became necrotic and foul smelling and were covered by a dirty gray membrane. Edema of the face appeared. This was apparently associated with the necrosis of the mucous membranes of the mouth. There were massive hemorrhages into the eyegrounds, with detachment of the retina of the right eye. On his ninth day in the hospital the patient died. The total duration of the illness was approximately thirty days.

*Necropsy*—There were numerous petechial hemorrhages into all the serous surfaces of the body and large and small hemorrhages into all the tissues of the body.

The spleen weighed 790 Gm. The cut surface was deep red and was peppered with enlarged, deeply purple malpighian bodies. Under the microscope it was seen that this appearance was due to the extensive extravasation of blood into the malpighian bodies. The normal architecture of this organ was obliterated. The sinusoids were distended, and the pulp was crowded with large round, oval or irregularly polyhedral cells with large eccentrically placed nuclei. The nuclei were oval, indented or folded over and hyperchromatic. The cytoplasm was slightly basophilic. Some of these cells contained acidophilic and others basophilic granules. An occasional mitotic figure was seen. In addition there were many cells resembling those of the myeloid series of the blood.

The liver weighed 1,600 Gm. The usual architecture was indistinct. The sinusoids were filled and markedly distended with mononuclear cells. The hepatic cords were narrowed owing to the crowding of the sinusoids, and in some zones the hepatic cells were necrotic, containing pyknotic nuclei. This was particularly evident in the periportal regions, where the cellular infiltration was most striking. The Kupffer cells in some zones appeared swollen. There was no increase in the amount of fibrous connective tissue.

All the abdominal, peritracheal and peribronchial lymph nodes were enlarged and deep red. When sectioned the cut surfaces were deep red, with small, scattered zones of yellow-white tissue. The usual architecture was almost completely effaced, and the follicles were obliterated. The sinusoids and surrounding tissues were heavily infiltrated with the characteristic mononuclear cells. Occasional mitotic figures were seen. Moderate numbers of small lymphocytes, a few neutrophils and eosinophils and an occasional large phagocytic cell also were present.

The bone marrow was hyperplastic, appearing red-brown. On section of the sternal marrow, hyperplasia of cellular elements was evident. There was great infiltration of the marrow with monocytes. While most of these cells appeared to be mature and most of the cells were identifiable, there were some smaller, less differentiated cells which were possibly reticular cells. Erythropoiesis was apparently normal, although it was not a striking part of the picture. Numerous myeloid cells in all stages of development, but with a preponderance of the more mature types, were present.

There was extensive invasion and infiltration with mononuclear cells of the heart, lungs, pancreas, adrenal glands, kidneys, thyroid gland, intestines, tonsils and other organs of the body. Areas of ulceration were present in the intestines, and on microscopic examination these were seen to be due to extensive invasion with the same cells.

CASE 4—W. H., a 56 year old white American farmer, married, was admitted to the Grace Hospital because of superficial injuries sustained one week before. He had been in good health until one month before his admission to the hospital,

when spontaneous suppurating ulcers appeared on the lateral aspect of the right thigh and ankle. He went to the New Haven Dispensary, where a diagnosis of leukemia was made on the basis of the examination of the blood, which showed red cells, 3,700,000, hemoglobin, 90 per cent (Dare), and leukocytes, 8,600, of which 7 per cent were neutrophils, 31 per cent lymphocytes and 62 per cent monocytes. Except for the local lesion, the physical examination revealed no abnormality. The patient refused to enter the hospital.

The previously described ulcers healed promptly, but three weeks before the patient's admission to the hospital a similar persistent ulcer appeared on the left ankle after trauma. One week before his admission to the hospital the patient was injured by a cow and was admitted because of pain, weakness and fever subsequent to the accident.

*Physical Examination*—The patient was emaciated. There were superficial bruises of the thorax. A few purpuric spots were diffusely present on the skin. Over the left external malleolus there was a suppurating ulcer. At the mucocutaneous junction of the mouth on the right side there was an ulcer about 5 cm in diameter covered with a dry brown crust. There were a few recent retinal hemorrhages. The teeth were all missing and the gums were not remarkable. There was slight inflammation of the pharynx. The cervical lymph nodes were slightly enlarged, but there was no other lymphadenopathy. There were signs of emphysema of the lungs. The edge of the liver was palpable, but the spleen could not be felt.

TABLE 2—Data on the Blood in Case 4

Date	Leukocytes	Neutrophils, %	Lymphocytes, %	Monocytes and Monoblasts, %
8/ 3	8,800	0	10	90
8/ 4	23,000	1	10	89
8/ 7	61,000	2	8	90
8/ 8	70,000	2	13	85
8/ 9	88,000	3	8	89
8/10	118,000	1	9	90
8/11	265,000	2	8	90
8/12	328,000	0	8	92

*Laboratory Examination*—The cells of the monocytic series were large and had abundant clear blue cytoplasm. Fine azure granules were present in the older forms, and in some of these there were vacuoles. Pseudopodic projections were numerous. The nuclei were leptochromatic and round, kidney shaped or actually lobulated. The proportion of cells classified as "blasts" increased rapidly, and in many of these there were nucleoli.

On the patient's admission to the hospital there were 4,400,000 red blood cells, and the hemoglobin value was 75 per cent, according to the Sahli standard. A reduction in the number of blood platelets was evident from an examination of stained smears. The erythrocyte count fell to 4,000,000 and the hemoglobin content to 62 per cent before death occurred.

Blood culture was sterile. The Wassermann reaction was negative. *Bacillus pyocyaneus* was recovered from the malleolar ulcer. On roentgen examination of the thorax enlargement of the hilar shadows and a localized area of rarefaction of the seventh rib on the left were noted.

*Clinical Course*—The temperature was 100 F when the patient was admitted to the hospital. Thereafter there were wide daily fluctuations with peaks as high as 104 F. Symptomatic treatment was of no avail, and the patient failed rapidly.

Five days before death the spleen became palpable. Nine days after admission to the hospital the patient died. The duration of the illness was slightly more than one month.

*Necropsy*—There were hemorrhages of varying extent into the skin, the organs of the body and the serous surfaces.

All the lymph nodes were enlarged and relatively soft in consistency. On section of a mediastinal node obliteration of the normal architecture was evident. The surface appeared mottled, and multiple hemorrhages were visible. A cavity approximately 1 cm in diameter, apparently the result of a previous hemorrhage, was seen. Diffuse, massive infiltration with large cells containing round, oval or reniform nuclei with a fine chromatin network and clear-staining cytoplasm was evident microscopically.

The spleen weighed 235 Gm. The cut surface was soft, pale gray and dotted with small areas of hemorrhage. The normal structure was obliterated by the massive invasion of cells the characteristics of which have been previously described.

The liver weighed 1,860 Gm. The surface was smooth, friable and mottled. Microscopically there were seen many small islands of the typical cells, and these were present also in considerable numbers between the columns of hepatic cells.

There was a striking decrease in the amount of normal fat in the bone marrow. Slight hyperplasia of the reticular tissue was evident. The normal cells of the bone marrow were displaced by an extensive uniform infiltration of large cells. These were characterized by their size and by large vesicular leptochromatic nuclei which were occasionally round but predominantly irregular or horseshoe-shaped. The cytoplasm was abundant, and only rarely were granules or vacuoles seen. Phagocytosis of cell fragments and pigment by these cells was occasionally seen. There was a scattering of eosinophils.

Cells of the myeloid series were only rarely encountered. Red blood cells were more abundant, but few normoblasts and megaloblasts were present. A scattering of blood platelets but no megalokaryocytes were seen.

The heart weighed 320 Gm. There were numerous subepicardial hemorrhagic spots, and in the pulmonary artery there was a large, jellylike grayish white thrombus which on microscopic examination was seen to be composed of a mass of monocytic cells bound together by small amounts of fibrin.

Infiltration with cells of the monocytic series was evident in the lungs, kidneys, adrenal glands and gastro-intestinal tract.

CASE 5—S. C., a 60 year old white widow, a housewife and practical nurse, entered the New Haven Hospital because of increasing weakness of six months' duration. In 1911 the patient had been operated on for strangulated hernia. Six months before the present admission to the hospital she fell, struck her head and lost consciousness. She dated her illness from this fall. Three months before her admission to the hospital, following a sore throat, rapidly progressing weakness and pallor were noted, and purpuric spots began to appear on the trunk and extremities. At this time fever developed and continued intermittently. Blurring of vision had been noted for four days, and two days before entering the hospital the patient became too weak to leave her bed.

*Physical Examination*—Pallor and cyanosis were striking. Numerous purpuric and petechial spots were present over the entire body. There was a large subconjunctival hemorrhage in the left eye. There were numerous retinal hemorrhages, some of which had white centers. The mouth was edentulous, but there were many small hemorrhages into the soft palate. The cervical, axillary and inguinal lymph nodes were slightly enlarged. There was dulness, with moist râles at the

bases of the lungs The area of cardiac dulness was moderately increased, and a systolic murmur was heard The blood pressure was 130 systolic and 80 diastolic The edge of the liver was felt about 1 cm and the spleen about 5 cm below the costal margin

*Laboratory Examination*—The blood was in group 3, according to the Jansky classification The Kahn test was negative The urine was normal, except for a slight trace of albumin

The red blood cell count was 1,400,000 per cubic millimeter, and the hemoglobin value was 20 per cent, of 154 Gm There were 203,000 leukocytes per cubic millimeter, of which 2 per cent were neutrophils, 32 per cent lymphocytes, 53 per cent monocytes and monoblasts, 2 per cent eosinophils, 1 per cent clasmotocytes (Sabin) and 10 per cent undifferentiated cells

The predominant cells were large, and all stages of development from the youngest monoblast to the mature monocyte were present The outline of the older cells was often irregular The cytoplasm of all the cells was abundant and stained a hazy powder blue Occasional Auer bodies were present in the immature cells The cytoplasm of the older cells contained a variable number of fine azurophilic granules The nuclei of the monoblasts were round or oval, and many contained nucleoli embedded in a homogeneous network of chromatin The more mature cells were characterized by typical oval or horseshoe-shaped nuclei In some the nucleus was distinctly irregular and sometimes lobed No evidence of phagocytosis was seen

*Clinical Course*—The temperature was 102 F, the pulse rate 100 and the respiratory rate 24 The patient was moribund when admitted to the hospital and shortly afterward lapsed into unconsciousness In twelve hours she died The duration of the disease was approximately six months

*Necropsy*—There were numerous petechial hemorrhages into the skin, mucous membranes, pleurae, diaphragm, liver, spleen and bladder The lymph nodes throughout the body were slightly enlarged, and the surfaces were deep red on section The usual architecture was distorted by large numbers of mononuclear cells, which filled the capillaries and sinusoids These cells contained large oval or bean-shaped, eccentrically placed nuclei The cytoplasm was abundant There was a slight general increase in the amount of reticulum

The spleen was moderately firm and weighed 530 Gm In some places the capsule was thickened, owing to infiltration with mononuclear cells The usual architecture was distorted, the malpighian bodies were indistinct, but the trabeculae were prominent The splenic pulp was filled with the previously described large mononuclear cells There was no increase in the amount of interstitial connective tissue

The liver weighed 2,025 Gm The usual architecture was preserved The sinusoids and periportal zones were crowded with large mononuclear cells The cells of the hepatic cords were not always clearly distinguishable

A section of the vertebral marrow gave evidence of extensive invasion by small round cells The normal hematopoietic tissue was almost completely obliterated by the process The predominant cells were somewhat larger than normal mature small lymphocytes The distribution of the chromatin resembled that often seen in lymphocytes, but the density of the nuclear staining was lighter than that of mature lymphocytes In the majority of the cells the cytoplasm was basophilic, and often the amount was small These cells, which had the appearance of immature elements, resembled the cells of the general reticulum, with varied

morphology and a tendency toward the formation of delicate cytoplasmic processes and occasionally syncytial sheets. They contained no phagocytosed material or vacuoles. No macrophages were seen.

Sections of the bone marrow were submitted to Dr R P Custer, of Philadelphia, who concurred in the general interpretation and in the diagnosis of monocytic leukemia.

CASE 6—E V, a white boy aged 16, entered Grace Hospital because of weakness. Seven months before his admission to the hospital he had begun to notice general malaise and easy fatigability. This continued for several months but was not severe enough to keep him from playing baseball and football. Two months before his admission to the hospital he injured his left knee and began to limp. This was followed by spontaneous migratory pain in the right knee and both shoulders. No swelling, redness or local heat was noted in the joints. Seven weeks before admission to the hospital he had a severe toothache, high fever and sweats. He also began to lose weight about this time and felt sick enough to

TABLE 3—Data on the Blood in Case 6

Date	Hemo globin, %	Erythro cytes, Thou sands	Leuko cytes	Poly morpho nuclears, %	Lym pho cytes, %	Mono cytes, %	Eosino phils, %	Comment
12/13/33	20	1,130	2,600	45	48	5	2	
12/14/33	Transfusion, 500 cc							
12/15/33	30	1,840	3,200	48	40	10	2	
12/18/33	Transfusion, 500 cc							
12/18/33			51,200	18	22	53	2	
12/19/33			57,200	13	30	57		
12/21/33			78,800	19	22	59		
12/26/33	50	3,140	105,000	12	53	35		Peroxi- 98% dase negative, 2% posi- tive, platelets 240,000
12/27/33	Transfusion, 500 cc							
12/28/33	50	2,980	37,000	11	58	31		
12/31/33	50	3,010	14,800	27	52	21		
1/ 2/34			13,800	10	51	37		
1/ 4/34	50	3,040	21,000	5	63	32		
1/ 6/34	Transfusion, 500 cc							
1/ 8/34	50	3,640	25,200	7	70	23		
1/11/34	50	2,050	63,600	2	18	80		
1/15/34	40	1,890	52,800	6	23	71		
1/18/34	50	3,160	78,600	6	38	56		

remain in bed. Two weeks before his admission to the hospital a tooth was removed, and this resulted in copious hemorrhage from the socket and persistent oozing for twelve days. From this time on he became much weaker, and pallor developed. There were periods of delirium. The past history revealed only pneumonia in 1932, an appendectomy in 1923 and "growing pains" as a child. The patient's mother had had tuberculosis, but no roentgen evidence of this process was noted in the patient or in other members of the family.

*Physical Examination*—Marked pallor and petechiae of the skin were noted. Emaciation was evident. The breath had a fetid odor. Retinal hemorrhages were present in the eyes. The gums were ulcerated and bleeding. The cervical and inguinal lymph nodes were enlarged, those of the anterior cervical chain having attained the size of pigeon eggs. There was hypertrophy of the heart, and a gallop rhythm and a to and fro murmur were heard at the apex. The lungs were normal, but there was elevation of the diaphragm on both sides. Both the liver and the spleen were large and extended downward to about the level of the umbilicus.

*Laboratory Examination*—A fairly advanced picture of hypochromic anemia with poikilocytosis, anisocytosis and polychromatophilia was seen. Platelets were

present in a greatly reduced number. A few normoblasts were seen. The monocytes were large cells which varied in size but averaged more than 16 microns in diameter. Practically all the cells were typically mature elements. The outline of the cells was often irregular, and in many instances actual pseudopods were apparent. The cells had abundant cytoplasm, in which were seen numerous fine azure-staining granules, for the most part grouped in the indentations of the nuclei. The nuclei were round, kidney shaped or actually lobulated. The chromatin network was delicate and evenly distributed. Nucleoli were seen only rarely. Cells that could be identified as clasmatocytes were not seen.

Biopsy of a large cervical lymph node revealed complete obliteration of the normal architecture by a massive infiltration of large round cells, with abundant cytoplasm and nuclei, which were round, kidney shaped or lobulated. These cells resembled closely the predominant cells of the peripheral blood.

Examination of the urine and feces revealed no abnormality. One blood culture showed *Staphylococcus aureus*, but this was thought to be due to contamination, because several later cultures proved sterile. Roentgenograms of the chest showed no abnormality. The bleeding and the clotting time were normal. The non-protein nitrogen content was 38 mg per hundred cubic centimeters of blood. The Kahn and Wassermann tests were both negative.

*Clinical Course*—Solution of potassium arsenite was administered, and four blood transfusions were given. At first the size of the lymph nodes seemed to decrease under treatment, but later they returned to the original size. The spleen and liver remained about the same. The temperature was irregular and of the "steep" type but was constantly high. The general course was steadily downhill. The patient left the hospital against advice and died about three weeks after discharge. The total duration of the illness was approximately nine months.

**CASE 7—C E**, a 62 year old Italian widow, entered the New Haven Hospital because of weakness and fever. She was known to have had elevation of the blood pressure for ten years. Beginning approximately two months before her admission to the hospital, weakness and progressive loss of weight were noted. During this period she lost about 20 pounds (9 Kg). One week before admission to the hospital she became unconscious for about ten minutes and fell to the floor. Subsequently she felt extremely weak, was feverish and complained of pain in the lower portion of the left side of the chest and neck.

*Physical Examination*—Malnutrition and dehydration were marked, and there was pallor of the skin and mucous membranes. The gums were boggy and red. The cervical lymph nodes were firm and slightly enlarged, other glands were not remarkable. Arteriosclerotic changes were evident in the retinal vessels and the peripheral arteries. There was a pleural friction rub, and signs of bronchopneumonia were noted at the base of the left lung. The heart was enlarged, the left border of cardiac dulness was in the anterior axillary line in the fifth interspace. A systolic murmur was heard over the entire precordium. The blood pressure was 120 systolic and 80 diastolic.

The abdomen was intensely distended, but both the liver and the spleen were moderately enlarged, and they were palpated below the costal margin.

*Laboratory Examination*—Hematologic data are shown in table 4. The cells classified as clasmatocytes varied in size. Some were no larger than the ordinary monocyte, but the majority were the largest cells seen and ranged from 20 to 30 microns in diameter. The outline of these cells was irregular and scalloped, and in some there were actual pseudopodia. The cytoplasm was a delicate pale blue with Leishman's stain and contained occasional vacuoles but few if any granules. The

nucleus was segmented into from two to twenty lobes connected by delicate strands and arranged in a radial cluster that resembled a bunch of grapes. The chromatin was condensed into irregular, heavy blotches which stained extraordinarily densely. In figure 3*B* a photomicrograph of one such cell is presented. On supravital study with neutral red and janus green these cells were seen to be motile, changing form more rapidly than the monocytes present. However, progression was slow, and in this particular they differed sharply from the neutrophils. The clasmatocytes contained many neutral red particles or vacuoles of various hues which ranged in size from small granules to bodies half as large as a lobe of the nucleus. Only an occasional janus green granule was seen.

When trypan blue was added to blood in vitro about 50 per cent of the cells took up the dye. Those classified as clasmatocytes contained an abundance of blue granules and vacuoles similar in size and configuration to the neutral red bodies.

As the disease progressed and the predominant cells became more immature, the percentage of cells taking up the dye decreased and the amount of dye in the

TABLE 4—Data on the Blood in Case 7

Date	Erythrocytes, Thousands	Hemoglobin, %	Leukocytes	Differential Count, Leishman Stain						Comment
				Neutrophils, %	Lymphocytes, %	Mononuclears, %	Myelocytes, %	Monoblasts, %	Clasmatocytes, %	
12/ 7	2,500	60	10,600							
12/ 8 a m			11,000	1	8	25	3	20	43	
12/ 8 p m	2,700	55	13,200							
12/ 9	2,000	52	25,600							
12/10	2,000	45		2	6			63	29	
12/ 8				12	14		8			Supravital differential count monocytes monoblasts and clasmatocytes, 66
12/ 9				2	16		26	22	34	

cells grew more scant. The monocytes had the usual motility and rosette arrangement of neutral red vacuoles. Many of the predominant cells, clasmatocytes and monocytes, took the peroxidase stain. There were anisocytosis and poikilocytosis of the erythrocytes, with occasional macrocytes and normoblasts.

The urine contained albumin (1 plus) and from 10 to 13 white blood cells per high power field. The feces were normal.

Stereoroentgenographic examination of the chest revealed elevation of the diaphragms, thickening of the pleurae and the presence of pleural effusion at the base and between the lower and the upper lobe of the left lung. There was evidence of a tumor in the upper portion of the mediastinum, with displacement of the trachea to the right.

The Kahn serologic test was negative. The nonprotein nitrogen content was 52 mg per hundred cubic centimeters of blood.

*Clinical Course*—The patient appeared chronically ill when admitted to the hospital. The temperature fluctuated between 102 and 105 F, the pulse rate between 110 and 140 and the respiratory rate between 22 and 40. Distention was intractable. Four days after admission to the hospital the patient lapsed into coma, and he died on the next day. Treatment had been entirely symptomatic. Permission for necropsy was not granted.

Although symptoms had been evident to the patient for only two months, it was thought probable that the duration of the disease had been appreciably longer. This case was unique in that there was a high percentage of cells identified on fixed smear and supravital studies as clasmotocytes.

CASE 8—M H, a 74 year old white American widow, was referred by Drs William Dennehy and Wilder Tileston. Early in June 1934 following removal of a tooth the patient's gums became swollen and ecchymotic, the inflammation extending to the cheek and neck of the affected side. The process was slow to subside, but after about three weeks the patient seemed entirely well again. Toward the end of July rapidly progressing weakness appeared, and the patient was forced to go to bed. Her appetite began to fail about this time, and marked pallor and loss of weight were noted. About one week after going to bed she began to complain of sore throat and vague abdominal distress. Previous to the present illness the patient had always been exceptionally well. Her family history was interesting in that one brother had died of Addison's disease and another recently of leukemia.

*Physical Examination*—On Aug 27, 1934, the patient was prostrate. Pallor was marked. The throat was red and edematous, but no ulcers were seen. The gums were not notable. The cervical lymph nodes were barely palpable, but there

TABLE 5—Data on the Blood in Case 8

Date	Erythrocytes, Thousands	Hemoglobin, %	Leukocytes	Poly morpho nuclears, %	Lymphocytes, %	Mono cytes, %
7/30	4,400	50	3,400			
8/14	4,400	50	23,000	5	20	75
8/21	3,000	45	120,000	5	10	85
8/26			14,000			

was no generalized lymphadenopathy. The liver was enlarged and could easily be felt about 4 cm below the costal margin. Although the spleen seemed large on percussion, it was not felt below the costal margin. The temperature was irregular in type, with a rise to 103 F in the evening and a fall to 101 F in the morning. The pulse rate was proportionately increased.

*Laboratory Examination*—The predominant cells were large, with homogeneous, abundant cytoplasm that looked like ground glass. A few fine azure granules were present, and these were often grouped in the indentations of the nuclei. The nuclei were round, oval, kidney shaped or actually lobulated. The chromatin was finely woven and homogeneous. No nucleoli were seen. The characteristic cells seemed mature, and while there was some variation in this respect, none was seen that could be classified as a monoblast. There were many smudges present. Anisocytosis and poikilocytosis of the red blood cells were marked. Many macrocytes were seen and an occasional normoblast and rare megaloblast. The blood platelets were definitely decreased in number.

On supravital examination the characteristic pseudopodic activity and motion of the monocytes were evident. Cytoplasmic vacuoles were frequently observed. There was evidence of phagocytosis by these cells, and in one instance a monocyte was actually seen engulfing a red blood cell.

*Clinical Course*—The patient failed rapidly and died on August 27. The course of the disease was probably between nine and twelve weeks.



## COMMENT

The eight cases of monocytic leukemia herein reported were characterized by an abrupt onset of symptoms and a relatively short course. The average duration of life after the onset of symptoms was three and one-half months, with a range from one to nine months. Case 1 is the second recorded instance of monocytic leukemia in a Negro, a previous case having recently been reported by Levine<sup>5</sup>. The ages of our patients ranged from 12 to 74 years, the latter being the oldest on record. In five cases the symptoms were first noted following extraction of teeth and in two instances following severe trauma. In all eight cases the first symptoms appeared between June and October. Seven of the eight patients lived in the country.

There seemed to be an association between the degree of monocytosis and the duration of the illness. In the cases of fulminating monocytic leukemia the number of monocytes in the peripheral blood was great or else increased to high levels rapidly, whereas in those in which the disease progressed more slowly the absolute number of monocytes was only moderately elevated. In case 2, in which the course was relatively long, there was a progressive decline in the absolute number of monocytes so that terminally leukopenia actually prevailed. During the last weeks of the illness it would hardly have been possible to establish a diagnosis of monocytic leukemia from the blood picture.

In accord with most of the cases previously reported general enlargement of lymph nodes was only slight, and the cervical chains were principally involved. When cervical lymphadenopathy was prominent it was associated with ulcerative lesions of the oral cavity. It is a question whether such lymphadenopathy may not have been in part due to hyperplasia secondary to necrosis and infection of the regional tissue. The spleen was enlarged in seven of the eight cases, but in all instances hepatomegaly was prominent.

Contrary to the observations of some investigators,<sup>8</sup> one or more nucleoli were seen in many of the monoblasts. Peroxidase-positive granules were identified in a variable proportion of the monocytes. The extent of the anemia and thrombopenia with resulting hemorrhagic manifestations was similar in degree to that seen in other forms of acute leukemia. Examination of the hematopoietic tissues, either at biopsy or at necropsy, furnished information sufficient to confirm the diagnosis of leukemia, but for the accurate identification of the cell type concerned repeated examination of blood spreads fixed and supravitaly proved of greater value.

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8 Weissenbach, R. J., Bourdillon, C., Martineau, J., and David, J. *Leucémie aigue a monocytes*, Sang **7** 371, 1933. Fowler, W. M. *Monocytic Leukemia*, J. Lab. & Clin. Med. **18** 1260 (Sept.) 1933.

# COMPARATIVE DIURETIC RESPONSE TO CLINICAL INJECTIONS OF VARIOUS MERCURIALS

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An increase in the flow of urine is produced by suitable doses of any of the mercurial compounds that have been studied with this in mind, but for therapeutic use certain organic compounds are employed almost exclusively at present, largely in order to avoid other actions of mercury, which are practically inevitable with the inorganic mercurials. That the diuretic potency of the organic compounds is superior is probably often assumed, but without adequate evidence. The few quantitative clinical data are very inadequate, and quantitative comparisons on animals also are scanty, as may be seen from the review by Fournau and Melville<sup>1</sup> (1931). These investigators confirmed with intravenous injections into rabbits the diuretic effect for all the inorganic and organic compounds of mercury which they tried, except colloidal suspensions, with quantitative differences that appeared related to the chemical constitution. Data on animals, however, cannot be transferred quantitatively to the clinic because of the difference in the dosage.

In our studies of the excretion of mercury in clinical treatment the urinary volume was always recorded, and thus a large number of data were accumulated, which seemed to furnish good material for a comparative study of diuretic potency. A preliminary report was made to the Federation of the American Biological Societies in 1930<sup>2</sup>. This report indicated not only that the flow of urine is increased by all forms of mercurial compounds used in the treatment of syphilis but that when

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This work was done under grants from the Therapeutic Research Committee of the Council on Pharmacy and Chemistry of the American Medical Association.

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1 Fournau, E., and Melville, K. I. Studies in Mercurial Chemotherapy Concerning Mercurial Toxicity, Its Evaluation, Mechanism, and Relation to Chemical Constitution, *J Pharmacol & Exper Therap* **41** 21 (Jan) 1931, Studies in Mercurial Chemotherapy Quantitative Evaluation of Mercurial Diuresis and Its Relation to Chemical Constitution, *ibid* **41** 47 (Jan) 1931.

2 Sollmann, Torald, and Schreiber, Nora E. The Diuretic Effects of Various Mercurial Treatments, *Am J Physiol* **93** 689 (June) 1930.

the comparison is based on the dosage and especially on the excretion of mercury the inorganic mercurial salts appear vastly more potent than the organic compounds, so much so that it was suggested that the diuretic action of the organic mercurial compounds may be due to the dissociation of a small amount of ionizable mercury. In the meantime, considerable additional data have become available, including data on several compounds not mentioned in the first study. As we have now terminated our investigations of the excretion of mercury, it is opportune to review and coordinate the entire mass of data on diuretic potency.

It may be assumed that patients studied were not dropsical, as are most of those who are subjected to the induction of mercurial diuresis as a therapeutic measure. This, however, is an advantage for quantitative comparison, indeed, it is indispensable, for ascites would introduce the serious complicating factor of wide variations in the excretable tissue fluid. It must also be noted that the intake of water was not controlled, the patients being entirely free to take liquids according to their thirst. This is often a more suitable way of studying diuresis, as it tends to keep the water content of the organism automatically on a more uniform level than does an arbitrary intake of fluid, which could only by rare accident avoid either forcing or restricting the amount of fluid imbibed beyond this level. The ideal of uniform conditions of experimentation may easily overshoot its mark. In this case, a uniform intake of fluid, even if it is carefully adjusted to an equilibrium in the individual patient in a preceding period, takes no account of the extra loss of fluid in the diuresis or of the wide variations in the loss of water by the skin caused by changes in temperature, etc. A uniform intake of water may be needed for a study of special problems, in general, however, the consumption of fluid *ad libitum* appears to be better justified as well as more convenient. It is misleading only if the intake of water is artificially altered by some intercurrent condition, but accidental variations of this kind generally balance each other in different patients. The *ad libitum* consumption of fluid had a further special advantage in the present inquiry in that it simulates more closely the conditions in dropsy, in which the blood may "drink" freely from the water reservoir of the effusions.

Variations in the quantity of the flow of urine should be compared on the basis of the departure from normal, the surplus and the deficit, rather than on that of the total water balance, for inclusion of the normal urinary volume artificially "dilutes" or minimizes the changes. The increase or "surplus excretion" was calculated both in cubic centimeters and as a percentage of the normal output. As these lead to the same general conclusions, only the percentage basis is cited in comparison.

of the data, for it is more rational and more consistent, an increase of 55 cc being much more important when it is added to a normal value of 10 cc than when it supplements one of 100 cc

#### EXPERIMENTAL MATERIAL

The data were collected in our investigation of the excretion of mercury after intravenous and intramuscular injections<sup>3</sup> The compounds may be grouped as follows, together with the dosage and intervals of administration and the number of patients and injections

1 *Organic Compounds*—Mercurosol (disodium hydroxymercurisaliciloxyacetate)<sup>4</sup> Intravenous—three patients, from ten to twelve injections of 5 cc of a 2 per cent solution (100 mg of the compound, equivalent to 43.4 mg of mercury) every second or third day

Intramuscular—three patients, from ten to twelve injections of 2 cc of a 2.5 per cent solution (50 mg of the compound, equivalent to 21.7 mg of mercury) every fourth or fifth day

Novasurol (Merbaphen) Intravenous—two patients, four injections, first injection, 0.75 cc of a 10 per cent solution (75 mg of the compound, equivalent to 25.42 mg of mercury), and subsequent injections, 1 cc of a 10 per cent solution (100 mg of the compound, equivalent to 33.9 mg of mercury) once a week

Intramuscular—three patients, from two to five injections, first injection, 0.75 cc of a 10 per cent solution (75 mg of the compound, equivalent to 25.42 mg of mercury), and subsequent injections, 1 cc of a 10 per cent solution (100 mg of the compound, equivalent to 33.9 mg of mercury) once a week

Salysgan Intravenous—three patients, from three to four injections, first injection, 0.75 cc of a 10 per cent solution (75 mg of the compound, equivalent to 28.2 mg of mercury), and subsequent injections, 1 cc of a 10 per cent solution (100 mg of the compound, equivalent to 37.6 mg of mercury) once a week

Intramuscular—three patients, from three to four injections, first injection, 0.75 cc of a 10 per cent solution (75 mg of the compound, equivalent to 28.2 mg of mercury), and subsequent injections, 1 cc of a 10 per cent solution (100 mg of the compound, equivalent to 37.6 mg of mercury) once a week

2 *Inorganic Ionizable Compounds*<sup>5</sup>—Mercuric Bromide Intramuscular—three patients, from eight to ten injections, 0.25 cc of a 4 per cent solution (10 mg of the compound, equivalent to 5.5 mg of mercury), three weekly injections followed by a series of injections, at first daily and finally spaced at longer and somewhat irregular intervals

Bichloridol (Mercuric Bichloride in Oil)<sup>6</sup> Intramuscular—three patients, from five to seven injections, injections from capsules, exact content of mercury unknown, but not less than 4.8 mg or more than 44.45 mg of mercury, injections twice a week

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3 Sollmann, Torald, Schreiber, Nora E., and Cole, H. N. Excretion of Mercury After Clinical Intramuscular and Intravenous Injections, *Arch Dermat & Syph* **32** 1 (July) 1935

4 Mercurosol has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association

5 This term is used rather loosely in the sense that the compounds yield reacting mercuric ions

6 Bichloridol has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association

Mercuric Oxycyanide Intravenous—three patients, from six to seven injections, 5 cc of a 0.2 per cent solution (10 mg of the compound, equivalent to 8.55 mg of mercury) twice a week

3 *Inorganic Colloidal Compounds*—Mercodel (Metallic Mercury) <sup>7</sup> Intravenous—three patients, four injections, first dose, 5 cc of a 6 per cent solution (300 mg of the compound, equivalent to 50 mg of mercury), second and third doses, 10 cc of a 6 per cent solution (600 mg of the compound, equivalent to 100 mg of mercury), fourth dose, 20 cc of a 6 per cent solution (1,200 mg of the compound, equivalent to 200 mg of mercury), weekly intervals

Mersulfol (Mercuric Sulfide) <sup>8</sup> Intravenous—three patients, from three to seven injections, 10 cc of a 2 per cent solution (200 mg of the compound, equivalent to 170 mg of mercury) twice a week

Intramuscular—five patients, from five to twelve injections, 3 cc of a 2 per cent solution (60 mg of the compound, equivalent to 51 mg of mercury), first patient, 10 cc twice a week for five injections, second patient, 10 cc three times a week for one week and then 3 cc per week for three weeks, three patients, 3 cc two or three times a week

4 *Unclassified Compounds*—Flumerin Intravenous—four patients, four injections, 10 cc of a 2 per cent solution (200 mg of the compound, equivalent to 65 mg of mercury) once a week for four weeks

Mercuric Salicylate in Oil Suspension Intramuscular—three patients, four or five injections, 1 cc of a 10 per cent solution (100 mg of the compound, equivalent to 60 mg of mercury) weekly

*Collection Periods*—The specimens of urine were collected uniformly for twenty-four hours before injection, and in the following periods after injection up to one hour, from one to two, from two to four, from four to eight, from eight to sixteen, from sixteen to twenty-four, from twenty-four to forty-two, from forty-two to sixty-six hours, and then for twenty-four hour periods

#### CORRELATION OF OBSERVATIONS AND DATA

To render the rather overwhelming mass of data manageable requires simplification and grouping whenever possible. The data are therefore presented as means, and the individual data are omitted, to avoid confusion and, incidentally, to economize on space. The hourly excretion in successive periods is a convenient starting point. Preliminary tabulations showed no marked trend in the diuresis caused by the successive weekly injections, and this makes it permissible to average the results of all the administrations of a given drug by a given channel. The hourly means may be most usefully presented in the form of curves, those for the intravenous injections in chart 1 and those for the intramuscular injections in chart 2. The time has been plotted logarithmically. The quantities, plotted vertically, are on a uniform scale for the urinary volume. The quantities of mercury varied through so wide a range that different decimal scales had to be employed, the magnification being

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<sup>7</sup> Mercodel has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association

<sup>8</sup> Mersulfol has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association

indicated on each chart. Inspection of these charts gives considerable information on the general features of the problem.

1 The first glance reveals the striking qualitative directional similarity in practically all the curves between the urinary volume, the excretion of mercury and the concentration of mercury for all the different compounds and for intravenous and intramuscular injections. With a few minor exceptions, all the quantities reach the peak within one or two hours of the time of injection, and then descend as parabolic curves, with fairly comparable speed. The chief difference is in the height of the peaks, and for the curve of urinary volume this has the moderate

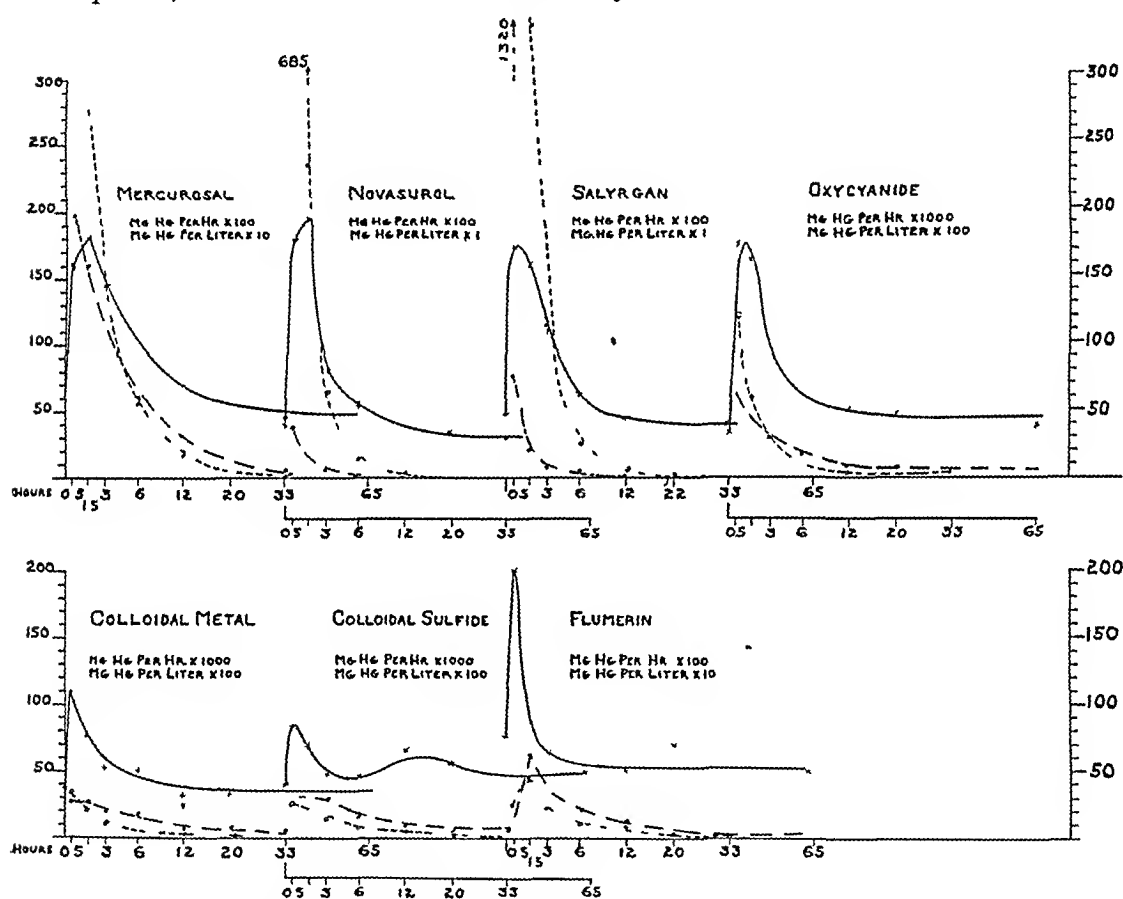


Chart 1—Curves of means for output of urine and mercury after the clinical injection of various compounds of mercury intravenously. The notation is explained in the text. In this and the following charts the time in hours is plotted logarithmically, and the unbroken line indicates the urinary output in cubic centimeters per hour, the line of short dashes the number of milligrams of mercury per hour and the line of short and long dashes the number of milligrams of mercury per liter.

range of from 2 to 5 times the normal level. The differences are much greater in the curves for mercury because of the great difference in the doses.

2 The curves for the mean urinary excretion produced by intravenous and intramuscular injections are almost quantitatively identical.

for most of the compounds, namely, salyrgan, mercurosal and the ionizable inorganic compounds. With novasurol the intramuscular injection causes a somewhat lower degree of diuresis, with colloidal mercuric sulfide the intravenous injection caused a distinctly lower degree of diuresis. It is notable that the diuresis caused by intramuscular injection is not materially slower than that caused by intravenous injection in any instance, but the excretion of mercury declines at a materially slower rate after intramuscular injection, at least with the organic compounds.

3 The diuretic effect of the therapeutic doses of the different compounds is of the same order of magnitude for all the organic and ion-

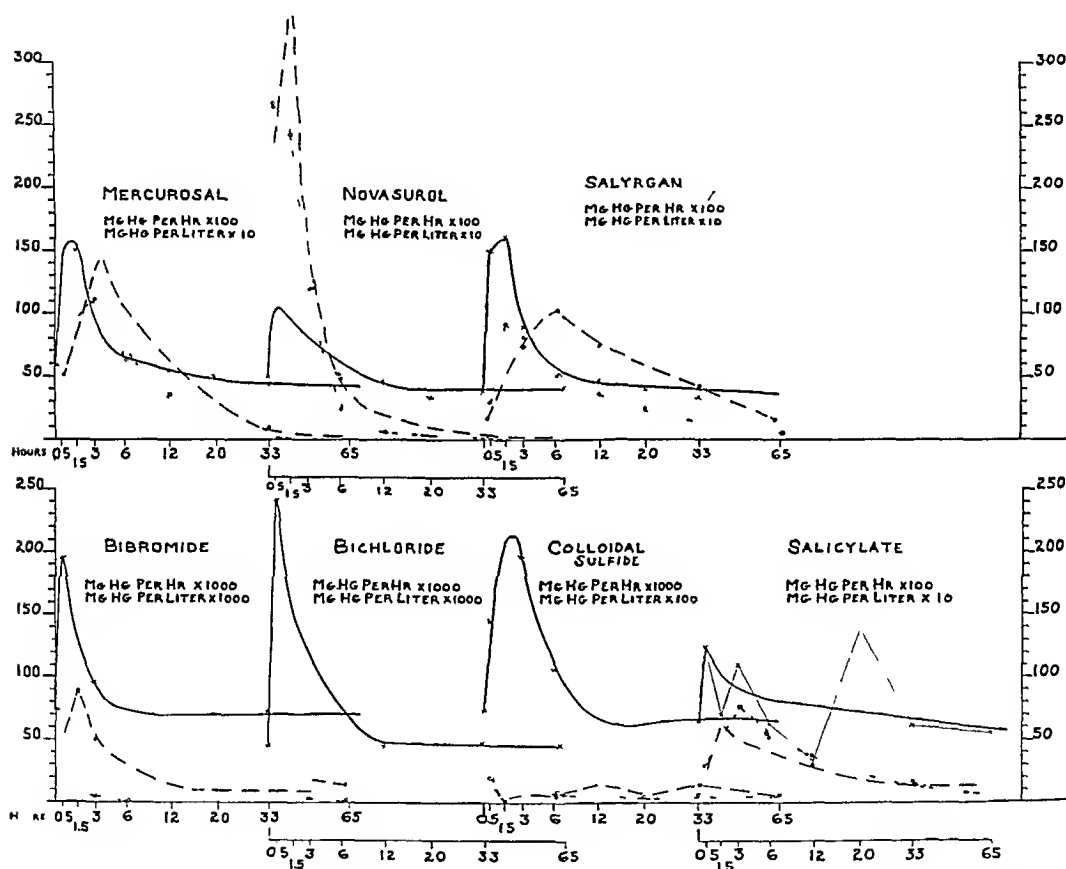


Chart 2—Curves of means for output of urine and mercury after the clinical injection of various compounds of mercury intramuscularly

izable inorganic compounds and flumerin. The colloidal suspensions injected intravenously and the salicylate in oil injected intramuscularly rank distinctly lower in magnitude of diuretic effect.

The most informative and significant events appear to be the total surplus excretion of urine, the maximal or peak excretion of urine, the rapidity of action when the peak is attained and the duration of action, represented by the slope of the degradation curve. These have been studied in relation to the urinary volume and to the dose, excretion and concentration of mercury.

*The Total Surplus and the Peak Excretion of Urine*—These may be conveniently presented together, as they generally, if not always, tend in the same direction. The total surplus excretion of urine expresses the total amount of surplus urine (i e., beyond the normal) excreted before the flow has returned to the normal level. The normal level was taken as the mean of the hourly output in the fore-periods and after-periods, for calculation of which were used the means obtained on the day before the injection and from eight to sixteen hours after the injection. The duration of the diuresis extends to the time when the urinary flow returns to the normal level, which may be read from charts 1 and 2. Multiplication of this time by the normal hourly urinary level gives what would be the normal volume of urine in the diuretic period, and subtraction of this normal volume from the observed volume gives the total surplus volume, in cubic centimeters, which may then be expressed as a percentage of the normal volume. These data are shown in table 1 *A*. This also gives the percentage reduced to the unit dose of mercury and of the excretion of mercury, which will be explained later.

*The Maximal or Peak Excretion of Urine*—The maximal or peak excretion of urine is the hourly urinary volume at the time of maximal diuresis. Like the total excretion of urine, it may be expressed as the actual rate and as the surplus rate, the latter in cubic centimeters and in percentage of the normal rate, and these again may be expressed as "crude surplus" and with reference to the dose and excretion of mercury. It is shown in table 1 *B*, which follows the same arrangement as table 1 *A* for total excretion of urine, and in which the columns are numbered to correspond with those in table 1 *A*. Although the intensity of the diuresis is so much greater in the peak period than in the total time of diuresis (column 6), the clinical benefits depend more on the total volume than on the volume of the peak. As shown in column 10, the amount of surplus fluid in the entire period of diuresis is from 1.3 to 8 times, averaging somewhat over 3 times, that removed in the peak hour.

*Surplus Excretion of Urine, In respect of the Ratio of Mercury*—For convenience in starting the analysis, the drugs may be combined into groups. For the total excretion of urine, expressed in percentage of the normal, the groups have the following sequence, in descending order:

Compound	Route	Percentage
Organic	Intravenous	78 to 122
Organic	Intramuscular	35 to 77
Colloidal	Intramuscular	62
Ionizable	Intravenous and intramuscular	35 to 46
Fluorim	Intravenous	}
Salicylate	Intramuscular	
Colloidal	Intravenous	
		36 to 20



TABLE 1—General Tabulation of the Median Values

	A Total Excretion of Urine *								
Column	1	2	3	4	5	6	7	8	9
Drugs	Single Dose, As Mercury, Mg	Duration of Surplus Excretion, Hr	Total Urinary Volume in This Time Ce	Normal Urinary Volume in This Time Ce	Surplus Urinary Volume in This Time Ce	Surplus, Percentage of Normal	Surplus, Percentage of Volume per Mg of Mercury Administered	Mercury Excreted During Period of Diuresis, Mg	Surplus Percentage per Mg of Mercury Excreted in Period of Diuresis
Intravenous									
Mercurosal	43 0	23	1,922	1,081	841	78 0	1 81	13 100	5 97
Novasurol	30 0	11	855	385	470	122 0	4 07	11 270	10 82
Salyrgan	35 0	17	1,224	680	544	80 0	2 29	20 370	3 92
Oxycyanide	8 5	16	1,107	768	339	44 0	5 11	0 320	137 00
Colloidal metal	100	20	862	720	142	20 0	0 20	0 140	143 00
Colloidal sulfide	170	8	431	416	15	3 6	0 021	0 110	32 70
Flumerin	65	16	1,006	816	190	23 0	0 35	2 110	10 90
Intramuscular									
Mercurosal	22	20	1,352	1,000	352	35 0	1 59	9 640	3 64
Novasurol	30	12	777	564	213	38 0	1 27	8 760	4 34
Salyrgan	35	13	946	533	413	77 0	2 20	6 720	11 40
Bibromide	5 5	10	812	600	212	35 0	6 35	0 083	1,160 00
Bichloridol		25	1,712	1,175	537	46 0		0 009	5,111 00
Colloidal sulfide	50	14	1,475	910	565	62 0	1 24	0 130	477 00
Salicylate in oil	60	13	833	650	183	28 0	0 43	3 540	7 90
	B Peak of Excretion of Urine								
Column	3	4	5†	6	7	8	9	10	
Drug	Peak of Urinary Volume per Hour, Ce	Normal Urinary Volume per Hour, Ce	Surplus Peak of Urinary Volume per Hour, Ce	Percentage of Normal Urinary Volume	Percentage per Mg of Mercury Administered	Mercury Excreted During Peak Hour, Mg	Peak of Urinary Volume per Mg of Mercury Excreted in Peak Hour, Percentage	Ratio of Total Surplus Excretion to Peak Surplus Excretion	
Intravenous									
Mercurosal	180	47	133	287	6 70	3 1800	90 2	6 3	
Novasurol	195	35	160	458	15 20	6 8500	68 8	30	
Salyrgan	175	40	135	337	9 60	13 2000	23 1	40	
Oxycyanide	175	48	127	265	30 60	0 1200	2,210 0	27	
Colloidal metal	105	36	69	192	1 90	0 0300	6,333 0	21	
Colloidal sulfide	83	52	31	60	0 35	0 0250	2,400 0	†	
Flumerin	200	51	149	293	4 50	0 4300	682 0	13	
Intramuscular									
Mercurosal	160	50	110	220	10 00	1 1100	197 0	32	
Novasurol	115	47	68	145	4 80	2 6600	54 5	31	
Salyrgan	160	41	119	291	8 30	0 9200	316 0	35	
Bibromide	195	60	135	225	41 20	0 0050	46,250 0	44	
Bichloridol	240	47	193	410		0 0025	160,000 0	28	
Colloidal sulfide	225	65	160	246	4 92	0 0200	12,300 0	35	
Salicylate in oil	125	50	75	150	2 50	0 4800	31 2	82	

\* The columns in parts A and B are numbered uniformly for analogous values

† The calculation of values is as follows: the value in column 5 equals that in column 3 minus that in column 4, the value in column 6 equals that in column 5 divided by that in column 4 and multiplied by 100, the value in column 7 equals that in column 6 divided by that in column 1, the value in column 9 equals that in column 6 divided by that in column 8, and the value in column 10 equals that in column 5, part A, divided by that in column 5, part B

‡ The total diuresis was so slight that the quotient would not be significant

The peak excretion is more uniform, so that the groups overlap and the sequence is somewhat confused, but broadly the compounds may be grouped as follows

Compound	Route	Percentage
Organic Ionizable	Intravenous Intramuscular	225 to 453
Flumerin Ionizable Colloidal	Intravenous Intravenous Intramuscular	
Organic Salicylate in oil	Intramuscular Intramuscular	145 to 291
Colloidal	Intravenous	
		60 to 192

In both the total and the peak excretion of urine the organic compounds administered intravenously stand highest, and the colloidal compounds administered intravenously, lowest. The results obtained with the others appear too much intermingled to invite generalization.

TABLE 2—*Ranking of the Individual Compounds on the Basis of the Surplus Excretion of Urine\**

Rank	A Total Surplus Excretion			For Equal Excretion of Mercury		
	For Therapeutic Dose			For Equal Dose of Mercury		
1	Novasurol V†	3 20	Bibromide M	5 200	Bichloridol M	1,173 00
2	Salysrgan V	2 10	Oxycyanide V	4 000	Bibromide M	267 00
3	Mercurosol V	2 05	Merbaphen V	3 200	Sulfide M	110 00
4	Salysrgan M	2 00	Salysrgan V	1 800	Colloidal metal V	33 00
5	Sulfide V	1 63	Salysrgan M	1 700	Oxycyanide V	31 00
6	Bichloridol M	1 21	Mercurosol V	1 400	Sulfide V	7 50
7	Oxycyanide V	1 16	Mercurosol M	1 250	Salysrgan M	2 60
8	Sulfide M	1 05	Novasurol M	1 000	Flumerin V	2 50
9	Novasurol M	1 00	Sulfide M	0 980	Novasurol V	2 50
10	Bibromide M	0 92	Salicylate M	0 340	Salicylate M	1 84
11	Mercurosol M	0 92	Flumerin V	0 280	Mercurosol V	1 37
12	Salicylate M	0 74	Colloidal metal V	0 160	Novasurol M	1 00
13	Flumerin V	0 61	Sulfide V	0 017	Salysrgan V	0 90
14	Colloidal metal V	0 52			Mercurosol M	0 84
Rank	B Peak Surplus Excretion			For Equal Excretion of Mercury		
	For Therapeutic Dose			For Equal Dose of Mercury		
1	Merbaphen V	3 20	Bibromide M	8 60	Bichloridol M	2,940 00
2	Bichloridol M	2 80	Oxycyanide V	6 50	Bibromide M	852 00
3	Salysrgan V	2 30	Merbaphen V	3 20	Colloidal sulfide M	226 00
4	Mercurosol V	2 00	Mercurosol M	2 10	Colloidal metal V	116 00
5	Flumerin V	2 00	Salysrgan V	2 00	Salysrgan M	58 00
6	Salysrgan M	2 00	Salysrgan M	1 70	Colloidal sulfide V	44 00
7	Oxycyanide V	1 80	Mercurosol V	1 40	Oxycyanide V	41 00
8	Colloidal sulfide M	1 70	Colloidal sulfide M	1 03	Flumerin V	13 80
9	Bibromide M	1 55	Merbaphen M	1 00	Mercurosol M	3 62
10	Mercurosol M	1 50	Flumerin V	0 94	Mercurosol V	1 66
11	Colloidal metal V	1 30	Salicylate in oil M	0 52	Merbaphen V	1 26
12	Salicylate in oil M	1 03	Colloidal metal V	0 40	Merbaphen M	1 00
13	Novasurol M	1 00	Colloidal sulfide V	0 07	Salicylate in oil M	0 57
14	Colloidal sulfide V	0 41			Salysrgan V	0 52

\* The compounds are arranged in each column in descending order of magnitude of potency. The quantities are expressed in multiples of values obtained with novasurol administered intramuscularly (as percentage of normal excretion of urine).

† V indicates intravenous and M intramuscular injection.

For comparison of the individual preparations it is convenient to use the results obtained with some familiar compound as a measure and to express the potency as multiples or fractions of this unit. The

mean values for novasurol injected intramuscularly were chosen for this purpose, but the conclusions would, of course, be the same if any other preparation were used as the basis for comparison. The sequence of the compounds, in descending order, and the values in this scale are shown in column 1 of table 2 for the therapeutic doses and in columns 2 and 3 for equal doses and equal excretion of mercury. With the therapeutic doses it may be remarked that novasurol administered intravenously, which heads the list, was 3 times as potent as the same preparation administered intramuscularly for both total and peak excretion of urine and that salyrgan was about twice as potent, both intravenously and intramuscularly, as novasurol injected intramuscularly by either criterion. The sequence of the three individual organic compounds is not the same for intravenous and for intramuscular injection. When given intravenously, novasurol was 1.5 times as potent as salyrgan, when administered intramuscularly, salyrgan was twice as potent as novasurol. Mercurosal ranks lowest for both routes, although not by a great distance. All the inorganic ionizable compounds induced an output of urine equal to or greater than that caused by novasurol injected intramuscularly. These statements apply equally to the total and to the peak excretion of urine, the figures for which agree closely (within one rank) for nine of the fourteen compounds. Colloidal mercuric sulfide injected intravenously and novasurol administered intramuscularly were ranked distinctly higher on the basis of the total excretion of urine, and bichloridol administered intramuscularly and flumerin and colloidal mercury injected intravenously were ranked higher on the basis of peak excretion. No generalization can be drawn from these exceptional shifts, as they may have been accidental. The general agreement of the sequence of total and peak excretion of urine is the significant feature of the comparison.

*Surplus Excretion of Urine Referred to Unit Dose of Mercury—*

The unit dose of mercury is shown in column 7 of table 1. For the total excretion of urine, the descending order of the compounds becomes

Compound	Route	Percentage
Ionizable	Intravenous and intramuscular	5.1 and 6.4
	Intravenous	1.8 to 4.1
Organic	Intramuscular	1.3 to 2.2
	Intramuscular	1.24
Colloidal	Intravenous	} 0.35 and 0.43
	Intramuscular	
Flumerin	Intravenous	} 0.02 and 0.2
Salicylate	Intramuscular	
Colloidal	Intravenous	0.02 and 0.2

This discloses an important shift in the rank of the inorganic compounds, which seem to be much more potent than the organic in a unit dose. Otherwise, the sequence remains the same. The groups are more widely separated, and the extremes do not overlap.

For the peak secretion of urine the descending order of potency of the compounds in unit doses is the same as for the total excretion, with the following values

Compound	Route	Percentage
Ionizable	Intravenous and intramuscular	31 and 41
Organic	Intravenous	7 to 15
Organic	Intramuscular	5 to 10
Flumerin	Intravenous	} 4.5 and 4.9
Colloidal	Intramuscular	
Salylate	Intramuscular	2.5
Colloidal	Intravenous	0.35 to 1.9

The sequence of the individual compounds on the basis of their potency in comparison with the potency of novasurol administered intramuscularly is shown in column 2 of table 2. The total excretion of urine produced by the inorganic compounds is 4 or 5 times that of novasurol administered intramuscularly with an equal dose of mercury. When injected intravenously novasurol is about 3 times, salyrgan 2 times and meicurosol  $1\frac{1}{2}$  times as potent as novasurol administered intramuscularly. For salyrgan and meicurosol the potency by intramuscular injection is very close to that by intravenous injection, in contrast to the widespread potency of novasurol. For the colloidal compounds the potency by intramuscular injection (0.98 times) is far greater than that by intravenous injection (0.017 and 0.16 times).

The peak excretion of urine shows the same sequence, the only shift of more than one position being for meicurosol administered intramuscularly, which has a higher position for the peak than the total excretion. The superior potency of the inorganic compounds is even more apparent in the figures for the peak (6.5 and 8.6 times that for novasurol administered intramuscularly) than in those for total excretion (4 and 5.2 times that for novasurol administered intramuscularly).

*Surplus Excretion of Urine Referred to Unit Excretion of Mercury*—This appears the most logical measure of potency, since it may be presumed to reflect the concentration of mercury in the blood with more certainty than does the dose, for the latter may be offset by differences in absorption and in the rate at which the compound leaves the blood stream. To establish this relation the total surplus excretion of urine was divided by the amount of mercury that had been excreted in the urine before the urinary flow had returned to the normal level, and, similarly, the amount of urine excreted at the peak of diuresis was divided by the amount of mercury excreted in the peak hour (table 1, column

9) The sequence of the group of compounds for surplus total excretion of urine is as follows

Compound	Route	Percentage
Ionizable	Intramuscular	1,160 to 5,111
Colloidal	Intramuscular	477
Ionizable	Intravenous	137
Colloidal	Intravenous	33 and 143
Flumerin	Intravenous	11
Salicylate	Intramuscular	8
Organic	Intramuscular	3.6 to 11.4
Organic	Intravenous	3.9 to 10.8

For surplus peak excretion of urine the sequence is

Compound	Route	Percentage
Ionizable	Intramuscular	46,250 to 160,000
Colloidal	Intramuscular	12,300
Colloidal	Intravenous	2,400 to 6,333
Ionizable	Intravenous	2,210
Flumerin	Intravenous	682
Organic	Intramuscular	55 to 316
Organic	Intravenous	28 to 90
Salicylate in oil	Intramuscular	31

The most striking feature of both sequences is the enormous superiority of the potency of the ionizable solutions to that of the organic compounds, the total excretion of urine being from 12 to 1,500 times greater and the peak excretion from 7 to 6,000 times greater. The colloidal compounds also are revealed as much more potent than the organic compounds, being from 3 to 130 times as potent for the total excretion of urine and from 8 to 440 times as potent for peak surplus excretions. In brief, on the basis of excreted mercury the organic compounds are so far inferior to the others as to justify the assumption that the diuresis caused by organic mercury is due to the liberation of small quantities of ionic mercury and that the molecule of organic mercury as such is very little, if at all, diuretic. Through this assumption, which is shared by Fournneau and Melville,<sup>1</sup> all diuresis caused by mercury would be reduced to a common basis.

In column 3 of table 2 is shown the sequence of the compounds in descending order on the basis of their potency in terms of novasurol administered intramuscularly. Mercury bichloride in oil administered intramuscularly ranks highest, both for total excretion of urine (1,170) and for peak excretion (2,940), next comes the bibromide administered intramuscularly (267 and 852) and third, the colloidal sulfide administered intramuscularly (110 and 226). The colloidal suspensions injected intravenously are 7.5 and 33 times as potent for total excretion of urine as novasurol administered intramuscularly and 44 and 116 times as potent for peak surplus excretion. For all these the superiority is greater for the peak than for the total excretion of urine, and the contrasts are much greater on the basis of excretion of mercury than on that of the dose of mercury. Among the organic compounds the spread is relatively small, for the total surplus excretion of urine the

spread being between 2.6 for salyrgan administered intramuscularly and 0.84 for mercuriosal administered intramuscularly, for the peak excretion salyrgan administered intramuscularly stands out with 58, the next highest is mercuriosal, 3.62, administered intramuscularly, with salyrgan, 0.52, administered intravenously. Salyrgan administered intramuscularly stands highest throughout, but the others intermingle without apparent order as to the compounds and the route of injection.

In a comparison of the ranking of dosage and excretion of mercury (by the positions in table 2) the bromide holds first or second place throughout, but most of the other compounds shift markedly and significantly, being essentially alike for total and peak excretion of urine.

TABLE 3—*Comparison of Surplus Excretion of Urine Following Intravenous and Following Intramuscular Injection of Various Compounds\**

	A Total Surplus Excretion		
	Therapeutic Dose	Equal Dose of Mercury	Equal Excretion of Mercury
	1	2	3
Mercuriosal	78/35 = 2.2	1.81/1.59 = 1.14	5.97/3.64 = 1.63
Novasurol	122/38 = 3.2	4.07/1.27 = 3.2	10.8/4.34 = 2.5
Salyrgan	80/77 = 1.04	2.29/2.20 = 1.04	3.92/11.4 = 0.34
Oxycyanide and dibromide	44/35 = 1.25	5.11/6.35 = 0.80	137/1,160 = 0.12
Colloidal sulfide	3.6/62 = 0.06	0.021/1.24 = 0.017	32.7/477 = 0.069
	B Peak Surplus Excretion		
Mercuriosal	287/220 = 1.3	6.7/10.0 = 0.67	90.2/197 = 0.47
Novasurol	453/145 = 3.4	15.2/4.8 = 3.2	68.8/54.5 = 1.3
Salyrgan	337/291 = 1.12	9.6/8.3 = 1.2	28.1/316 = 0.09
Oxycyanide and dibromide	265/225 = 1.2	30.6/41.2 = 0.74	2,210/46,250 = 0.05
Colloidal sulfide	60/160 = 0.37	0.35/4.92 = 0.07	2,400/12,300 = 0.195

\* The percentage of surplus excretion is based on the formula: value for intravenous injection divided by value for intramuscular injection equals quotient.

The changes may be summed up thus, that the organic compounds have a relatively higher potency on the basis of dosage and the colloidal suspensions (including flumerin) have a higher potency on the basis of excretion. This is equivalent to saying that the mercury of the organic compounds is less diuretic than that of the colloidal compounds, and this again is merely saying that the organic mercury as such is, at least relatively, inactive. Colloidal mercury is presumably equally inactive, but it does not circulate long in this form, nor is it excreted in this form.

*Comparison of the Diuretic Potency of Intravenous and Intramuscular Injections*—A priori, it would probably be assumed that compounds should have greater potency when injected intravenously, especially for the peak excretion of urine. Analysis of the data shows that this assumption would generally be wrong. In table 3 the relative

diuretic potency of intravenous and intramuscular injections is shown as the quotient  $\frac{V}{M}$ . Column 1, in which the dose is not taken into account, has little significance. Column 2, showing the results for equal doses of mercury is the most important practically. The columns show that only novasurol has a materially higher potency when injected by vein than when injected by muscle, with a quotient of 3.2 for both total and peak surplus excretion of urine. The quotients for mercurosal and salyrgan range between 1.2 and 0.67 for peak excretion and nearer 1 for total excretion, probably within the range of accidental variation. For the inorganic compounds the potency on intramuscular injection somewhat surpasses that on intravenous injection, with  $\frac{M}{V}$  equaling 1.25, for total excretion of urine and 1.33 for peak excretion. With the colloidal sulfide, the superiority of the intramuscular over the intravenous route is marked, with  $\frac{M}{V}$  equaling 60 for total and 14 for peak excretion of urine. This may be due to rapid flocculation of the solution when injected intravenously, which would make it relatively ineffective.

On the basis of the amount of mercury excreted (column 3 of table 3), novasurol is again distinctly more effective when injected intravenously, with  $\frac{V}{M}$  equaling 2.5 for total and 1.3 for peak excretion of urine. The superiority is therefore not as marked as on the basis of the equal doses. The potency of mercurosal is irregular, with the intravenous route superior ( $\frac{V}{M}$  equaling 1.63) for total excretion of urine and inferior (0.47) for peak excretion. In the case of salyrgan the intramuscular route is markedly more effective, with  $\frac{M}{V}$  equaling 3 for total and 11 for peak excretion of urine. For the inorganic compounds the superiority of the intramuscular route also becomes more marked with  $\frac{M}{V}$  equaling 8 for total and 20 for peak excretion, for colloidal sulfide the superiority of the intramuscular route persists but is less marked,  $\frac{M}{V}$  equaling 15 for total and 5 for peak excretion.

In a review of all the data on the comparison of the potencies of compounds administered by the intravenous and intramuscular routes, it is notable that the potency of a compound when given intravenously is inferior to that of the compound when given intramuscularly more often than it is superior (in the four columns of table 3, the potency on intravenous administration is greater 8 times and the potency on intramuscular administration 12 times). Only novasurol was consistently superior in potency on intravenous injection. The superiority of intramuscular injection was most marked for the injections of the colloidal compounds, presumably because when injected intravenously these compounds rapidly become inactive owing to flocculation. For the

inorganic ionizable and for the organic compounds the superiority of intramuscular injections is generally markedly greater on the basis of equal excretion of mercury than on that of equal doses of mercury, and somewhat greater for peak than for total surplus excretion of urine

*Speed and Duration of the Diuretic Action, or the Slope of the Degradation Curve*—Tabulations were made of the hour when the diuresis and the output and concentration of mercury reached their peak and of the number of hours between these peak values and the times when the surplus excretion of urine, the output of mercury per hour and the concentration of mercury had returned by one-third, one-half, two-thirds and entirely to the normal level

The means for all the observations on all the compounds form a convenient point of departure. They are given in table 4 and figure 3. This shows graphically that the speed and duration of the three factors

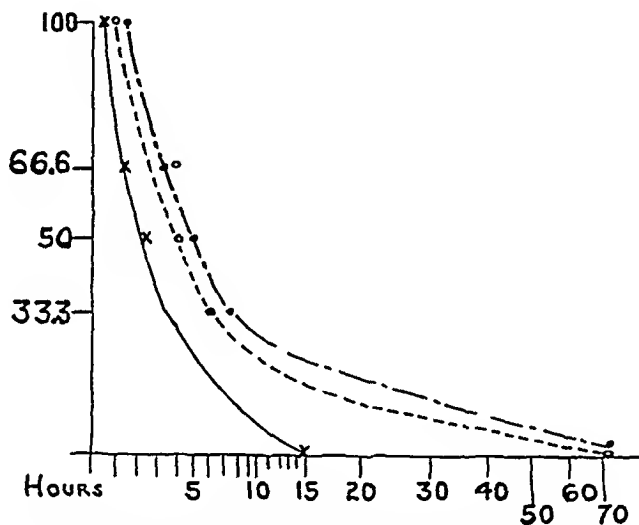


Chart 3—Curves of degradation of surplus excretion of urine and of excretion of mercury from peak to zero, with means of all the observations on all the compounds

—surplus excretion of urine, the amount of mercury and the concentration of mercury—run closely parallel. The two curves for mercury are almost identical, and that for urinary output differs only in that the curve is degraded almost twice as rapidly.

Comparison of the individual compounds in table 5 shows the mean time of the peak and of the half-degradation and return to normal. The one-third and two-thirds degradation times also were tabulated and compared but are not reproduced, since the half-degradation adequately represents the whole sequence of degradation, and is least subject to accidental distortion. The concentration of mercury is shown but will not be discussed, since the concentration of mercury in the blood stream would be reflected more consistently in the amount of mercury excreted at the given moment than by its concentration in the urine.



As the peak is generally attained within one or two hours, the unit of hour periods permits only a coarse classification. The peak of urinary volume was attained within an hour by twelve of the fourteen methods of administration of seven compounds intravenously and of seven intramuscularly. Of these, with seven there had already been a material decline in the second hour and with five in the third hour. With only

TABLE 4—General Means of the Peaks of Excretion and Degradation Times

	Surplus Excretion	Mercury per Hour, Mg	Mercury per Liter, Mg
Hours to peak	< 1 hour	10	12
Hours from peak to one third return	15	37	34
Hours from peak to one half return	21	40	44
Hours from peak to two thirds return	31	63	72
Hours from peak to normal	150	720	720

TABLE 5—Means for Individual Compounds for Peaks of Excretion and Degradation Times

Drug	Surplus Excretion			Urinary Excretion of Mercury per Hour			Urinary Mercury per Liter		Peak Levels		
	Injection to Peak, Hr	Peak to Half Level, Hr	Peak to Normal, Hr	Injection to Peak, Hr	Peak to Half Level, Hr	Peak to Normal, Hr	Injection to Peak, Hr	Peak to Half Level, Hr	Surplus Excretion, Cc per Hr	Mercury, Mg per Hr	Mercury, Mg per Liter
Intravenous											
Mercurosol	1 to 2	4.9	23	0 to 1	3.70		0 to 1	4.20	133	3.1800	19.50
Novasurol	0 to 2	2.7	11	0 to 1	1.75	72	0 to 1	1.75	160	6.8500	38.10
Salyrgan	0 to 2	2.6	17	0 to 1	1.70	72	0 to 1	1.70	135	13.2000	75.40
Oxycyanide	0 to 2	2.0	16	0 to 1	2.00	16	0 to 1	2.00	127	0.1200	0.69
Colloidal mercury	0 to 1	1.7	20	0 to 1	3.00	8	0 to 2	11.40	69	0.0300	0.28
Colloidal sulfide	0 to 1	1.5	8	0 to 2	5.20	24	0 to 4	9.30	31	0.0250	0.31
Flumernin	0 to 1	1.0	16	1 to 2	4.00	132	1 to 2	4.80	149	0.4300	6.30
Intramuscular											
Mercurosol	0 to 2	1.9	20	2 to 4	9.70	103	2 to 4	11.70	110	1.1100	14.80
Novasurol	0 to 1	2.2	12	0 to 2	3.30	103	1 to 2	3.50	68	2.6600	35.10
Salyrgan	0 to 2	2.7	13	1 to 2	11.80	103	4 to 8	33.10	119	0.9200	10.20
Bibromide	0 to 1	1.3	10	0 to 2	4.00	24	1 to 2	4.40	135	0.0050	0.09
Bichloridol	0 to 1	2.0	25	2 to 4	7.60		2 to 4	10.80	193	0.0025	0.02
Colloidal sulfide	2 to 3	3.8	14	0 to 1	5.00		0 to 1	1.70	160	0.0150	0.14
Salicylate in oil	0 to 1	3.0	13	1 to 2	11.30	144	1 to 2		75	0.4800	6.85

two was more than an hour required to attain the peak of urinary volume, viz, with mercurosol injected intravenously the peak was reached between one and two hours, and with colloidal sulfide administered intramuscularly, in from two to three hours. The distribution of the other peaks does not show any apparent orderly relation as to compounds or route of injection.

The attainment of the peak of excretion of mercury per hour, on the other hand, is distinctly faster after intravenous than after intramuscular injection, with six of the seven compounds injected intra-

venously and with only three of the seven compounds injected intramuscularly, the peak was reached within an hour, and with none of those injected intravenously but with two of those injected intramuscularly, viz, mercurosals and bichloridol, more than two hours was required. The distribution of the individual compounds does not show any apparent orderly relation.

*Correlation of Time of Attainment of Peak and Degradation*—This is shown by the following means of time (the figures in parentheses show the number of compounds represented in each quantity)

To Peak, Hours	Half Degradation Surplus Excretion of Urine, Hours	Mercury Excreted per Hour, Hours
0.1	1.8 (7)	2.8 (6)
0.2	2.4 (5)	4.2 (3)
1.3	4.4 (2)	
2.4		8.9 (5)

The correlation is significant for both diuresis and excretion of mercury. It is explained by the assumption that slower absorption or mobilization of active mercury means that a longer time is required to reach a peak and that the mercury continues to be active longer after the peak has been passed.

*Comparison of Peak Level and Half-Degradation Time*—When the data for each class are arranged in the order of height of peak, there is no concordance in any of the factors (urinary volume, amount and concentration of mercury) between the height of the peak and the time of degradation. It may therefore be considered as definitely settled that the height of the peak has essentially no influence on the rate of degradation. This dispenses with the need of considering dosage in the further treatment of the data.

*Group Study of Half-Degradation Time*—This is shown in table 6, which indicates the following generalizations. There is little, if any, difference between the mean values for intravenous and those for intramuscular injections as regards the duration of diuresis, but the excretion of mercury is markedly more prolonged with intramuscular injections. This prolonged excretion of mercury holds true for the intramuscular injection of both the organic and the ionizable inorganic compounds, but the associated diuresis appears distinctly shorter, especially that for the organic compounds. The colloidal suspensions show the reverse effect. The period of diuresis following intramuscular injection is markedly longer than that following intravenous injection, and the difference in the excretion of mercury is relatively small.

The inorganic ionizable compounds produce a briefer duration both of diuresis and of excretion of mercury than do the organic compounds, by either route.

The colloidal compounds injected intravenously cause the shortest period of diuresis of all the compounds, except flumerin, and the longest period of excretion of mercury of all the compounds injected intravenously

The colloidal suspensions injected intramuscularly cause the longest period of diuresis of all the compounds and the shortest period of excretion of mercury of all the compounds injected intramuscularly

TABLE 6—*Mean of Half-Degradation Time by Groups in Hours from the Peak*

Compounds	Surplus Excretion	Mercury, Mg per Hour	Mercury, Mg per Liter
All Mean	1 to 49 21	17 to 118 4	17 to 331 44
All (intravenous injections) Mean	1 to 49 20	17 to 52 29	17 to 114 37
All (intramuscular injections) Mean	13 to 39 23	33 to 118 74	17 to 331 76
Organic (intravenous injections) Mean	22 to 49 32	17 to 37 24	17 to 42 26
Organic (intramuscular injections) Mean	19 to 27 23	33 to 118 83	35 to 331 161
Inorganic (intravenous injections)	20	20	20
Inorganic (intramuscular injections) Mean	13 to 20 17	40 to 76 58	44 to 108 76
Colloidal (intravenous injections) Mean	15 to 17 16	30 to 52 41	93 to 114 104
Colloidal (intramuscular injections)	39	50	17
Flumerin	10	40	48
Salicylate in oil (intramuscular injections)	30	113	

TABLE 7—*Ranking of Compounds According to Half-Degradation Time in Ascending Order*

Rank	Surplus Excretion	Hours	Mercury per Hour	Hours	Mercury per Liter	Hours
1	Flumerin	V 10	Salyrgan	V 170	Salyrgan	V 170
2	Bibromide	M 13	Novasurol	V 175	Colloidal sulfide	M 170
3	Colloidal sulfide	V 15	Oxycyanide	V 200	Novasurol	V 175
4	Colloidal metal	V 17	Colloidal metal	V 300	Oxycyanide	V 200
5	Mercurosol	M 19	Novasurol	M 330	Novasurol	M 350
6	Bichloridol	M 20	Mercurosol	V 370	Mercurosol	V 420
7	Oxycyanide	V 20	Flumerin	V 400	Bibromide	M 440
8	Novasurol	V 22	Bibromide	M 400	Flumerin	V 480
9	Novasurol	M 22	Colloidal sulfide	M 500	Colloidal sulfide	V 930
10	Salyrgan	V 26	Colloidal sulfide	V 520	Bichloridol	M 1080
11	Salyrgan	M 27	Bichloridol	M 760	Colloidal metal	V 1140
12	Salicylate in oil	M 30	Mercurosol	M 970	Mercurosol	M 1170
13	Colloidal sulfide	M 39	Salicylate in oil	M 1130	Salyrgan	M 3310
14	Mercurosol	V 49	Salyrgan	M 1180	Salicylate	M

The ranking of the individual compounds by half-degradation time from quickest to slowest is shown in table 7. The following particulars may be added to the generalization of the group rankings

For surplus excretion of urine practically all the organic compounds give results somewhat below the mean value. The values for intramuscular and intravenous injections rank close together, except for those

for mercurosal, with which the diuresis following intravenous injections lasts over 25 times that following intramuscular injection. The values for colloidal suspensions injected intravenously, including flumerin, show diuresis of short duration, while the period of diuresis following the intramuscular injection of colloidal mercuric sulfide is one of the most prolonged. The action of mercuric salicylate also is slow.

For the excretion of mercury (per hour) the most striking feature is the shorter duration following the intravenous injection, which has been discussed. The distribution of the individual compounds according to rank appears to be irregular, with little relation to their ranking for diuresis, twelve of the fourteen compounds differ by more than one rank, indicating that some feature other than the gross circulation of mercury is concerned in the diuresis, presumably ionization. It is curious that the period of diuresis after the intravenous injection of salyrgan ranks with the shortest and that after the intramuscular injection of this compound, with the longest.

TABLE 8—*A Comparison of the Half-Degradation Time of the Compounds After Intravenous and After Intramuscular Injection\**

	Surplus Excretion	Mercury per Hour
Mercurosal	49/19 = 2.6	37/97 = 0.38
Novasuroil	27/22 = 1.2	175/33 = 0.53
Salyrgan	26/27 = 0.96	17/118 = 0.14
Oxycyanide and dibromide	20/13 = 1.5	20/40 = 0.50
Colloidal sulfide	15/38 = 0.40	52/50 = 1.04

\* The figures are based on the formula: values for intravenous injections divided by values for intramuscular injection equals quotient.

The relative duration (half-degradation) of the diuresis and of the excretion of mercury produced by intravenous and intramuscular injection of the individual compounds is shown as quotients in table 8.

#### SUMMARY AND CONCLUSIONS

A series of organic, inorganic and colloidal compounds of mercury injected intramuscularly and intravenously in clinical practice were compared as to diuretic response. Observations on the peak of excretion of urine and the total surplus output of fluid were found to lead to the same general conclusions.

The organic compounds cause somewhat greater diuresis in therapeutic doses, but with reference to the dose of mercury, and especially to the amount of mercury excreted, the organic compounds are far surpassed both by ionizable inorganic and by colloidal compounds. The superiority of the ionizable compounds is so marked that it suggests that the diuretic action of all mercurial compounds may be due to the liberation of some mercury ions.

Reactions to intramuscular and those to intravenous injections do not differ consistently in degree, speed or duration of diuresis, although the excretion of mercury is more rapid following intravenous injections

Practically all the curves for urinary output and excretion of mercury have a similar form, except that the curve for urinary output declines about twice as rapidly as that for the excretion of mercury

The rapidity of ascent and descent of the curves for both urinary output and excretion of mercury tends to vary in the same direction, but the height of the maximal level of urinary output or of excretion of mercury has no consistent effect on the duration

The organic compounds cause somewhat more prolonged periods of diuresis and excretion of mercury than the inorganic compounds, injected both by vein and by muscle. The colloidal compounds cause the shortest period of diuresis when injected by vein and the longest period of excretion of mercury when injected by muscle. They cause the longest period of diuresis and the shortest period of excretion of mercury

The differences among the compounds of each group are minor and do not suggest a significant generalization

# UNTOWARD EFFECTS OF DIURESIS

WITH SPECIAL REFERENCE TO MERCURIAL DIURETICS

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The syndrome to be discussed in this paper is seen in connection with diuresis and is characterized by preliminary symptoms of weakness, restlessness and mental confusion (sometimes progressing to delirium and psychosis), which may be followed by apathy, coma and in some cases death. The turgor of the tissues may become poor, the tongue exceedingly dry and thirst extreme. In some instances the premonitory symptoms of restlessness and confusion do not appear, the syndrome being ushered in by apathy. Simple though profound weakness often follows marked diuresis, and when it occurs alone, it is not to be considered as an alarming or serious symptom. It is the mildest expression of this clinical picture but is not significant because the organism automatically reestablishes its equilibrium after a longer or shorter time. Any or all of these phenomena may appear concomitantly with complications inherent in the underlying disease process or in association with other superimposed complications. However, they are often distinguishable even in the face of these confusing factors and, in any event, should be borne in mind when a patient who has been subjected to diuretic therapy appears to be failing.

There is nothing new in this syndrome as described. Eichhorst<sup>1</sup> in 1898 was able with digitalis and theobromine sodiosalicylate to produce marked diuresis, after which somnolence, disorientation, delirium and apathy developed in certain cases. Sprague and Graybiel<sup>2</sup> mentioned a case of malignancy with ascites in which they thought that death was hastened by the marked effect of salyrgan. Srnetz<sup>3</sup> in 1934 stressed the necessity for care in administering salyrgan to patients

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From the service of Dr. George Baehr, Mount Sinai Hospital

1 Eichhorst, H. Toxämische Delirien bei Herzkranken, *Deutsche med Wchnschr* **24** 389 (June 23) 1898

2 Sprague, H. B., and Graybiel, A. Salyrgan as a Diuretic. Report of Sixty Cases, *New England J Med* **204** 154 (Jan 22) 1931

3 Srnetz, K. Vorsicht mit Salyrgan bei schwerer Herzschwäche, *München med Wchnschr* **81** 1891 (Dec 6) 1934

with severe cardiac insufficiency and mentioned somnolence and mental confusion following diuresis

It is important to emphasize that the clinical picture herein described may conceivably be produced without the use of mercurial diuretics and that in no sense are these observations to be taken as an indictment of these valuable drugs. Qualitatively, though not quantitatively, the xanthines<sup>4</sup> produce the same effect as the mercurials. Even in spontaneous diuresis, such as may occur when a patient with cardiac decompensation is put to bed, there is a loss not only of water but of sodium chloride as well. If the intake of salt and water is then unduly restricted, the condition which we have already described may develop, despite the fact that diuretic drugs have not been used. Other disorders involving the depletion of water and salt may present similar features.

However, the problem which is presented has assumed greater importance in the past decade, since it was during this period that the mercurial diuretics were introduced into general use. Although the symptoms we have described are not in any sense pathognomonic of a condition caused by salyrgan and allied drugs, these phenomena are so intimately bound up with their use that any discussion of the problem must necessitate a discussion of the mercurial diuretics as well. This syndrome is more likely to occur when mercurial diuretics are used, since their ability to cause rapid dehydration is more marked than that of any other available diuretic agent.

The facts which are most pertinent to the problem are as follows

1 It has been shown that in diuresis due to salyrgan and related drugs there is a huge excretion of sodium chloride and water<sup>5</sup> (Cha-

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4 Blumgart, H. L., Gilligan, D. R., Levy, R. C., Brown, M. G., and Volk, M. C. Action of Diuretic Drugs, *Arch. Int. Med.* **54**: 40 (July) 1934.

5 The clinical picture already outlined calls to mind the weakness, apathy and coma seen in the acute crises of Addison's disease, which may be precipitated by deprivation of sodium (Loeb, R. F., Atchley, D. W., and Stahl, J. The Role of Sodium in Adrenal Insufficiency, *J. A. M. A.* **104**: 2149 [June 15] 1935). It is interesting to note that the syndrome of heat cramps (Talbot, J. H. Heat Cramps, *Medicine* **14**: 323 [Sept.] 1935) is also associated with a diminution of the sodium content of the blood, although clinically it appears to have little in common with the acute collapse of Addison's disease and the syndrome herein described.

Blumgart has shown that sodium, potassium and calcium are excreted in the urine in the same proportion in which they occur in blood plasma and extracellular fluids, i. e., 145 milliequivalents of sodium, 4 milliequivalents of potassium and 4 milliequivalents of calcium per liter. During the period of induced diuresis he found no alterations of these constituents in the blood, chloride, however, was excreted in larger amounts than the basic ions (190 milliequivalents) and in some instances was associated with an initial period of hypochloremia. On the first day after diuresis there was almost complete retention of available sodium chloride.

banier, Lebert and Lumière,<sup>6</sup> Keith, Barrier and Whelan,<sup>7</sup> and Blumgart<sup>4</sup>)

2 The degree of diuresis is dependent on the amount of the mercurial administered. When the dose of merbaphen is increased from 1 to 2 cc there is a threefold increase in the excretion of water and sodium chloride and a twofold increase in the duration of the action (Blumgart<sup>4</sup>)

3 The greater the diuresis, the longer the time required by the body to regain its fluid<sup>4</sup>

4 The larger the subject, i e., the greater the available amount of body fluid, the greater the diuretic response<sup>8</sup>

5 To overcome the emaciation associated with diuresis in experimental animals (used for determining minimal toxic doses of mercurials) Fournneau and Melville<sup>9</sup> found that fluid administered by mouth was more effective than that given parenterally. This confirmed Gunsberg's previous work<sup>10</sup>

In *The Journal of the American Medical Association* for Sept 15, 1934,<sup>11</sup> in the section on "Queries and Minor Notes" a question is asked concerning the untoward effects after the fifth and sixth injections of salyrgan. The following quotations from the answer are pertinent:

Mercurial diuresis is intimately associated with the available sodium chloride and during mercurial diuresis large quantities of sodium chloride are eliminated in the urine. When salyrgan is used, the sodium chloride reserves of the body often become depleted, particularly if the patient is on a low sodium chloride intake.

Furthermore, some authors have felt that following sodium chloride depletion in the body further doses of salyrgan may give reactions as a result of hypochloremia.

We believe that the sodium ion may prove to be an important factor in these cases, since in patients receiving ammonium chloride and cal-

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6 Chabanier, H., Lebert, M., and Lumiere, F. Analyse physiologique de l'action du 440-B (ou neptal), *Bull Soc franç d'urol* **6** 259 (Dec 19) 1927

7 Keith, N. M., Barrier, C. W., and Whelan, M. The Diuretic Action of Ammonium Chloride and Novasurol in Cases of Nephritis with Edema, *J A M A* **85** 799 (Sept 12) 1925

8 Blumgart and others<sup>4</sup>. The presence of edema is no assurance that the patient is not suffering from salt and water deprivation. He may complain of great thirst and present poor turgor of the tissues over the upper half of the body. The mechanism of this clinical fact is a moot point.

9 Fournneau, E., and Melville, K. I. Studies in Mercurial Chemotherapy I. Concerning Mercurial Toxicity, Its Evaluation, Mechanism, and Relation to Chemical Constitution, *J Pharmacol & Exper Therap* **41** 21, 1931

10 Gunsberg, H. Diureseversuche, *Arch f exper Path u Pharmacol* **69** 381, 1912

11 Treatment of Cardiac Decompensation, *Queries and Minor Notes*, *J A M A* **103** 858 (Sept 15) 1934



cium chloride as adjuvants to diuresis some, if not all, of the chloride ion is replaced, yet they may also show some or all of the symptoms we have described. In fact, a state of acidosis may be produced with depression of the carbon dioxide of the blood (case 1). In any event, the sodium ion seems to be most important for the replacement and retention of water in the intercellular spaces<sup>12</sup>

As has already been mentioned, when a patient who is subjected to dehydration therapy begins to fail, the explanation is often difficult in view of the underlying disease processes and complications usually found in such subjects. One must endeavor to decide whether any of the following factors are present and, if so, whether they are etiologic, contributory or only incidental to the clinical picture: (1) irremediable myocardial insufficiency, (2) fresh coronary thrombosis, (3) exacerbation of rheumatic carditis, (4) pulmonary infarction, (5) infection of the respiratory tract, (6) true renal insufficiency,<sup>13</sup> (7) cerebral vascular accident, (8) excessive use of sedatives and (9) the syndrome dealt with in this paper.

The eighth possibility is of great importance, as the edematous patient with myocardial insufficiency is often extremely restless and large doses of sedatives are required to induce quietude and thus spare the myocardium. The stupor induced by rapid dehydration is too readily attributed to the use of sedatives (see case 2).

A study of our case reports and of those recorded by other observers provides no entirely adequate basis for the prediction and exclusion of patients unfavorable for drastic dehydration therapy. As stated previously, the following factors should be taken into consideration, and particular care should be exercised in their presence: old age, advanced atherosclerosis<sup>14</sup> and cachexia. The renal function, as determined by the concentrating power of the kidneys, is important (Saxl<sup>15</sup>). The

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12 Fishberg, A. M. *Hypertension and Nephritis*, ed. 3, Philadelphia, Lea & Febiger, 1934.

13 If hypochloremia is present, the histologic picture of the kidneys may be confusing, since the kidney in a case of pyloric obstruction—another condition associated with hypochloremia—and the kidney in a case of mercurial disease present similar features, namely, tubular degeneration and calcification (Brown, G. E., Eusterman, G. B., Hartman, H. R., and Rowntree, L. G. *Toxic Nephritis in Pyloric and Duodenal Obstruction. Renal Insufficiency Complicating Gastric Tetany*, *Arch. Int. Med.* **32**: 425 [Sept.] 1923; Zeman, F. D., Friedman, W., and Mann, L. T. *Kidney Changes in Pyloric Obstruction*, *Proc. Soc. Exper. Biol. & Med.* **21**: 179, 1923).

14 Reference should be made to the poor prognosis in patients over 45 years of age with diabetic coma, dehydration and vasomotor collapse in Lande's series (Lande, H. *Uncontrollable Causes of Death in Diabetic Coma*, *J. A. M. A.* **101**: 9 [July 1] 1933) and to case 3 of our series.

15 Saxl, P. *Letale Quecksilberintoxikation nach einmaliger Novasurol Injektion*, *Wien. klin. Wchnschr.* **16**: 437, 1925.

test dose should be small, since the diuretic response is a function of the dose (Blumgart<sup>4</sup>) One point of warning should be included here If the test dose is ineffective and thoracentesis or paracentesis is then performed, a subsequent injection of the diuretic drug may produce a too dramatic and undesirable result, which is thought to be due to improvement of the cardiac action in the former instance and to improvement of the renal circulation in the latter This should be borne in mind before one proceeds with the second injection Furthermore, it is important to dehydrate the patient gradually, if possible, since the more rapid and drastic the dehydration, the longer and more difficult it is for the organism to regain its water and sodium chloride equilibrium<sup>4</sup> Finally, one should avoid carrying out too many procedures (such as phlebotomy, thoracentesis, paracentesis abdominis and the administration of diuretic drugs) at one time This admonition applies particularly in the case of patients of advanced age with predominating failure of the right side of the heart, ascites, pleural effusions and subcutaneous edema

If, despite these precautions, untoward symptoms develop, therapy should be begun as soon as the syndrome we have discussed is diagnosed or suspected It consists of the following measures

- 1 The administration of water—by mouth if possible
- 2 The administration of sodium chloride by mouth, at first in capsules and later as a 0.1 per cent solution, which is effective in the restoration of the sodium content of the blood<sup>16</sup>
- 3 Parenteral administration, if the foregoing methods are impossible The intravenous and subcutaneous methods of treatment are not as effective as the oral route

If therapy is delayed, the condition is no longer reversible and may end fatally

#### REPORT OF CASES

CASE 1—R. F., a 57 year old woman, at the time of admission to the hospital had edema of the legs and abdominal wall, dyspnea and orthopnea The diagnosis was generalized arteriosclerosis with coronary involvement, myocardial insufficiency and hypertension After dehydration therapy, which included the administration of ammonium chloride and neptal (an addition product of mercury acetate and salicylamino-allylacetic acid)<sup>17</sup> (15 cc intramuscularly), she lost 32 pounds (14.5 Kg) The carbon dioxide content of the blood, which was 58 volumes per cent when the patient was admitted to the hospital, fell to 44.5 volumes per cent As the congestive phenomena improved, the patient showed mental confusion and restlessness, which persisted for eight days Though there were no focal neuro-

16 Talbott, J. H. Heat Cramps, *Medicine* **14** 323 (Sept.) 1935

17 The various mercurial diuretics mentioned in these case reports were supplied in the form of approximately 10 to 13.5 per cent aqueous solutions

logic signs and despite the fact that there were no mental changes while there was severe decompensation, the condition was attributed to cerebral arteriosclerosis plus cardiac decompensation. No further injections of mercurial diuretics were given. Although the general dehydration measures were not discontinued, the patient recovered.

Fifteen months later the patient was readmitted to the hospital because of increasing decompensation for five weeks. She received three injections of mercupurin (an addition product of theophylline and a mercurated propyl derivative of a camphoric amine) over a period of eighteen days, with resulting pronounced diuresis. She then complained of profound weakness, began to act peculiarly and refused to cooperate. Eighteen days after her readmission to the hospital she went into vasomotor collapse, the clinical picture resembling that of acute coronary thrombosis, though without electrocardiographic changes as compared with previous records. Fluids were forced, and in the next three days the patient's condition improved remarkably, so that she was discharged from the hospital in one month.

In this case restlessness, mental changes and a period of vasomotor collapse occurred during dehydration therapy. By omitting further injections of neptal during the patient's first stay in the hospital and by forcing fluids during her second stay, recovery was obtained.

CASE 2—G M, a 65 year old man, entered the hospital complaining of dyspnea and orthopnea of four months' duration. The diagnosis was generalized arteriosclerosis with coronary involvement, auricular fibrillation, chronic bronchitis and emphysema and myocardial insufficiency. The patient was placed on a dehydration regimen, which included three injections each of 2 cc of salyrgan, administered one day, one week and two weeks, respectively, after the patient's admission to the hospital. During the first two weeks of his hospital stay he lost 30 pounds (13.6 Kg) in weight and complained of severe weakness and diarrhea. Four days later stomatitis and pharyngitis developed, and there was a slight rise in temperature. The patient became unresponsive and uncooperative, refusing food and fluids. The symptoms were at first ascribed to the use of chloral hydrate. However, during the following three days fluids were forced, the stomatitis and diarrhea subsided and the patient became more responsive and cooperative. He was permitted to gain several pounds, and there was no evidence of congestive failure. One month after his admission to the hospital he was able to be discharged. This is an instance of severe weakness and uncooperativeness following drastic diuresis. It is probable that the symptoms of diarrhea and stomatitis were due to mercurialism, although this feature of the case was not investigated. It should be remarked further that the untoward symptoms were at first attributed to the use of chloral hydrate, which had been exhibited only in average doses. With the administration of fluids in liberal amounts recovery ensued.

CASE 3—R H, a 73 year old woman, entered the hospital because of dyspnea, orthopnea and edema. The diagnosis was generalized arteriosclerosis, coronary arteriosclerosis, auricular fibrillation, myocardial insufficiency with pulmonary congestion, hepatic congestion and edema of the legs. On dehydration therapy, including two injections of neptal, each of 15 cc, given one and four days after her admission to the hospital, the patient lost 25 pounds (11.4 Kg) in weight. Her convalescence was interrupted by a period of drowsiness, which, in view of the evident dehydration, was attributed to the vigorous diuretic measures. When all medication except digitalis was discontinued and the intake of fluids was increased, the patient improved remarkably and did not gain any weight. She was discharged improved one month after her admission to the hospital.

In a subsequent admission eighteen months later, the patient was acutely ill but alert, talkative and cooperative. She had had symptoms of congestive failure for four weeks. Diuresis was established with mercupurin. On the following day severe weakness and drowsiness developed. These symptoms were combated with fluids administered hypodermically and intravenously. However, the general condition grew worse rapidly, the patient went into peripheral circulatory collapse, was obviously dehydrated and had a terminal temperature of 107.6 F.

During the patient's first stay in the hospital a period of drowsiness followed dehydration. During her second stay diuresis was rapidly followed by circulatory collapse and terminal hyperpyrexia.

CASE 4—J. V., a 65 year old man, entered the hospital because of myocardial insufficiency due to disease of the coronary arteries. He was placed on dehydration therapy, which included 1 cc of salyrgan given intravenously. Although the patient's original weight was only 94 pounds (42.7 Kg.), there was pronounced diuresis. The following day he became noisy and irrational and had delusions of persecution requiring the administration of morphine and chloral hydrate. Progressive weakness ensued, and the patient was obviously dehydrated. Fluids were forced, but he became stuporous and died with a terminal temperature of 101.4 F.

This case illustrates the point that a patient with a small body weight, i. e., with a small reserve of salt and fluid, should be dehydrated cautiously.

CASE 5—M. K., a 65 year old woman, was admitted to the hospital with complaints of dyspnea and edema. The diagnosis was generalized arteriosclerosis, including coronary arteriosclerosis, myocardial insufficiency, hydrothorax on the right and edema of the legs. The patient was placed on dehydration therapy and received three injections of mercupurin, each of 2 cc. She lost 38 pounds (17.3 Kg.) in weight over a period of twelve days. When signs of decompensation had disappeared and the patient was ready to be out of bed, she became drowsy and uncooperative, refusing food, fluids and medication. When fluids were forced, these symptoms cleared up, and the patient was able to leave the hospital much improved one month after her admission. The same sequence of events had been observed on two previous admissions.

This case is one in which drowsiness and lack of cooperation regularly followed the period of dehydration.

CASE 6—A. S., a 68 year old woman, was admitted to the hospital with symptoms of progressive dyspnea and orthopnea, which had been increasing for three months. The diagnosis was generalized arteriosclerosis, coronary arteriosclerosis and myocardial insufficiency with hydrothorax on the right. The patient was immediately placed on dehydration therapy, including digitalis and 2 cc of neptal. When admitted to the hospital she was verbose but entirely rational, dyspneic and orthopneic. In three days there was a loss of 10 pounds (4.5 Kg.). On the third day, the temperature rose to 103 F., and the patient became intensely cyanotic and unresponsive. The following morning she became irrational, and soon thereafter she died. In this case the sudden change which occurred after three months of cardiac decompensation was coincidental with and probably attributable to the rapid dehydration therapy.

CASE 7—A 67 year old man entered the hospital complaining of exertional precordial pain of ten years' duration and dyspnea and edema of four months' duration. The diagnosis was generalized arteriosclerosis, with cerebral and coronary involvement and myocardial insufficiency. With sedatives and dehydration therapy, including the restriction of salt and fluid, and two intramuscular injections of mercupurin (1 and 2 cc, respectively), the patient lost 30 pounds (13.6 Kg.).

Thirteen days after his admission to the hospital and one day after the second injection of mercupurin was given it was noted that the patient was suffering from marked weakness. The following day mental aberration developed, and he became noisy and attempted to strike the nurses. It was necessary to transfer him to another institution. This case is an instance of weakness and psychosis, diagnosed at the time as "psychosis with cardiac disease" following diuresis.

#### SUMMARY

A clinical picture which may be seen in association with diuresis is described.

The syndrome consists of the following features: weakness, restlessness, mental confusion, apathy, coma and, in some instances, death. All of these features need not be present in a given case.

The syndrome is attributed primarily to the depletion of water and sodium chloride.

The therapy consists in the restoration of water and sodium chloride, preferably by mouth.

Certain criteria and methods of prophylaxis are suggested. It is stressed that no indictment of the mercurial diuretics or of the various methods of dehydration is intended.

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# FUNCTION OF THE LARGE INTESTINE OF MAN IN ABSORPTION AND EXCRETION

STUDY OF A SUBJECT WITH AN ILEOSTOMY STOMA AND AN  
ISOLATED COLON

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The object of this study was to determine the function of the large intestine as an excretory organ and to consider its probable rôle in absorption under normal conditions. The opportunity for such a study was presented by a young woman who had been subjected to a single barrel permanent ileostomy which had left an isolated large intestine. At operation the ileum, which had been severed close to the ileocecal junction, had been brought out through the abdominal wall. Hereditary polyposis of the colon had constituted the indication for this operation, which had been performed as a preliminary measure to colectomy. This procedure permitted the collection of the excreta of the small intestine, and the products of the isolated colon could be recovered at the same time. In this manner it was possible to determine the composition of the intestinal material that normally is delivered to the large intestine and, by comparison with normal feces, to estimate the changes usually produced by the colon during alimentation. Furthermore, collection of material which originated in the isolated colon during known metabolic periods made it possible to test the validity of current conceptions of the colon as an excretory organ. If the chief value of the intestine in man is in excretion and if this portion of the intestine plays an important part in the excretion of calcium, magnesium and iron, as is stated in textbooks of physiology,<sup>1</sup> an analysis of the products of this isolated colon might reveal such specific functions. The stomach and small intestine of this subject were normal, and, although the colon contained polyps, it

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1 Starling, E H Principles of Human Physiology, ed 6, Philadelphia, Lea & Febiger, 1933, pp 1 and 136

seems reasonable to assume that a specific function of the colonic epithelium in excretion of minerals would not be affected, particularly since a great deal of normal mucous membrane was present and since the pathologic alterations did not suggest an accompanying diminution in the functional ability of the epithelial cells

#### THE PLAN OF STUDY

The subject of this study was a woman aged 21 who weighed 100 pounds (45.4 Kg) and who was 60¾ inches (154.3 cm) in height. She enjoyed excellent health. During her stay in the hospital collections of the total urine, ileostomy dejecta and colonic products were made during periods in which the total intake was constant and of known amount. For purposes of analysis the collections were divided into three lots, each lot representing the collections made in three days. Carmine markers were used to separate the feces which were passed from the ileum in each period.

TABLE 1—*Food Eaten in Different Periods*

Type of Food	Amount, Gm		
	Period 1	Period 2	Period 3
Banana	69	50	50
Orange juice	100	100	100
Tomato juice	100	100	100
Carrots	50	50	50
Bread	55	30	60
Oatmeal	100	50	50
Potato	87	50	50
Rice	100	50	50
Milk	167	100	100
Cream, 20 per cent	180	100	150
Eggs	167	50	50
Steak	94	100	100
Butter	29	40	60
Sugar	22	5	5
Jelly			30
Coffee	181	100	100
Sodium chloride	5	3.5	3.5
Ferrous sulfate		0.3	0.3
Distilled water, cc	1,000	1,000	1,000
Calories	1,914	1,138	1,573

*Procedure for the Intake*—The daily intake of food was identical for each day of one three day period, but a change was made for each period. This food, which had a low salt content, was prepared in the same way each time. It was weighed and was entirely consumed. Salt (pure sodium chloride) was added in weighed amounts. The food eaten daily during the three periods is listed in table 1. One thousand cubic centimeters of distilled water also was given every day. All the food was cooked in aluminum vessels to avoid contamination with iron, as it was desired to estimate the amount of iron in the collections. During the last two periods 60 mg of iron was administered daily by mouth in the form of ferrous sulfate. The intake for twenty-four hours was analyzed for each period. For analysis the food was prepared with that which was served to the patient. A homogeneous suspension of the total diet was made and determinations of the nitrogen, fat and chlorides were obtained with the wet preparation, which obviated the possibility of loss by drying. A large aliquot was dried. Portions of this were converted to ash in the usual manner in platinum dishes, using a muffle furnace with a temperature kept below 500 C. The cal-

cium, magnesium, phosphorus, sodium and potassium in the ash were extracted with hydrochloric acid. For the determination of iron another sample of the food was dried in the presence of sulfuric acid and ashed in a silica dish. The iron was extracted with sulfuric acid. This extract was treated with hydrogen sulfide to remove the copper before the amount of iron was estimated.

*Procedure for the Dejecta from the Ileostomy*—The excretions from the abdominal stoma were collected in a rubber pouch the contents of which were removed at intervals, a measured amount of distilled water was used to transfer the contents to suitable containers, which were immediately placed on ice. Carmine markers proved most efficient for the separation of the feces. A homogeneous suspension of the total dejecta was then made, and aliquot portions of the fresh wet substance were analyzed for nitrogen, chloride, fat and carbohydrate. A portion was dried, and aliquot portions of this dry material were converted to ash in a manner similar to that employed in the analysis of the

TABLE 2—*Chemical Methods Used*

For nitrogen	Kjeldahl's macro method
For chloride	Volhard's titration with sulfocyanate indicator after digestion with nitric acid in the presence of silver nitrate <sup>2a</sup>
For fat	A modification of the Saxon method <sup>2b</sup>
For carbohydrate	Hydrolysis with hydrochloric acid, the Shaffer-Hartmann-Somogyi method was used on a phosphotungstic acid filtrate <sup>2c</sup>
For phosphorus	Method of Fiske and Subbarow <sup>2d</sup>
For calcium	Method of Tisdall and Kramer <sup>2e</sup>
For magnesium	Magnesium was determined on the filtrate which was left after the determination of the calcium, the magnesium was precipitated as magnesium ammonium phosphate, according to the method of Tisdall and Kramer, and a colorimetric determination of phosphate was made by the method of Fiske and Subbarow
For potassium	Preprecipitation with cobalt nitrate and titration with potassium permanganate, according to the method of Tisdall and Kramer
For sodium	Butler and Tuthill's <sup>2f</sup> application of the method of Barber and Kolthoff <sup>2g</sup>
For iron	Titration with titanium sulfate, according to the method described by Klumpp <sup>2h</sup>

food. Determinations of calcium, sodium, phosphorus, potassium, magnesium and iron were made on extracts (table 2). The chemical methods referred to in table 2 are described in the literature <sup>2</sup>

2 (a) Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 829. (b) Saxon, G. J. A Method for the Determination of the Total Fats of Undried Feces and Other Moist Masses, *J. Biol. Chem.* **17**: 99-102, 1914. (c) Shaffer, P. A., and Somogyi, Michael. Copper-Iodometric Reagents for Sugar Determination, *ibid.* **100**: 695-713 (May) 1933. (d) Fiske, C. H., and Subbarow, Y. The Colorimetric Determination of Phosphorus, *ibid.* **66**: 375-400 (Dec.) 1925. (e) Tisdall, F. F., and Kramer, Benjamin. Methods for the Direct Quantitative Determination of Sodium, Potassium, Calcium, and Magnesium in Urine and Stools, *ibid.* **48**: 1-12 (Sept.) 1921. (f) Butler, A. M., and Tuthill, Elizabeth. An Application of the Uryal Zinc Acetate Method for Determination of Sodium in Biological Material, *ibid.* **93**: 171-180 (Sept.) 1931. (g) Barber, H. H., and Kolthoff, I. M. A Specific Reagent for the Rapid Gravimetric Determination of Sodium, *J. Am. Chem. Soc.* **50**: 1625-1631 (June) 1928. (h) Klumpp, T. G. The Determination of Iron in Biological Materials, *J. Biol. Chem.* **107**: 213-223 (Oct.) 1934.



*Procedure for the Urine*—The twenty-four hour collections of urine were preserved with thymol. Daily estimations of the creatinine were made to serve as an additional check on the accuracy of the collections. Determinations of the chloride, nitrogen and inorganic phosphorus were made directly on the urine. An ash was prepared for determinations of sodium, potassium, calcium, magnesium and iron. Two thousand cubic centimeters of urine was used for the iron determination.

*Procedure for the Colon*—After it had been ascertained roentgenographically with a barium sulfate enema that the colon filled easily, it was cleaned out at the beginning of the metabolic period with repeated enemas of warm distilled water, and the return flow was discarded. At the end of three days the process was repeated until the return flow was clear. The fluid was saved. This procedure was repeated at the end of nine days, and the contents were saved. The first collection was made at the end of period 1, and the second collection was

TABLE 3—*Analysis of the Intake and Output of a Subject with an Ileostomy Stoma*

	Average Daily Value, Gm										
	Nitro gen	Fat	Carbo hydrate as Dex trose	Water	Phos phorus	Chlo ride	Sodium	Potas sium	Magne sium	Cal cium	Iron
Period 1, diet 1 (3 days)											
Intake	10.28	121	142.0	2,188		4.34	3.54	2.75	0.187	0.579	0.0144
Urine	7.52			1,070	0.767	2.93	1.02	2.32	0.065	0.274	0.0003
Ileal dejecta	1.37	8		305	0.202	0.57	0.97	0.12	0.097	0.287	0.0075
Output	8.89		6.7	1,375	0.969	3.50	1.99	2.44	0.162	0.561	0.0078
Balance	+1.39	+113	+135.3	+813	+0.141	+0.84	+0.55	+0.31	+0.025	+0.018	
Period 2, diet 2 (3 days)											
Intake	6.50	67	93.0	1,782	0.650	2.91	1.69	1.95	0.132	0.322	0.0693
Urine	7.70			1,022	0.708	2.11	0.51	1.95	0.061	0.202	0.0002
Ileal dejecta	1.19	5		341	0.122	0.74	1.03	0.10	0.064	0.164	0.0566
Output	8.89		4.2	1,363	0.825	2.85	1.54	2.05	0.125	0.366	0.0563
Balance	-2.39	+62	+88.8	+419	-0.175	+0.06	+0.15	-0.10	+0.007	-0.044	
Period 3, diet 3 (3 days)											
Intake	7.10	99	126.0	1,734	0.759	3.06	1.74	1.94	0.142	0.377	0.0737
Urine	7.31			843	0.553	1.96	0.13	1.88	0.057	0.208	0.0001
Ileal dejecta	1.33	6		393	0.171	0.73	1.32	0.17	0.077	0.202	0.0611
Output	8.64		5.5	1,236	0.724	2.69	1.45	2.05	0.134	0.410	0.0612
Balance	-1.54	+93	+120.5	+498	+0.035	+0.37	+0.28	-0.11	+0.008	-0.033	

made at the end of the two subsequent periods. The material obtained was grayish white, and the odor was similar to that of feces. There was no gross blood in the specimens, and their appearance was similar to that of the rectal discharges which the patient had been having on every second or third day before the study was begun. The stools that were passed by rectum without the use of an enema in a later period of two weeks, during which the intake was not controlled, also were analyzed.

## RESULTS

*The Dejecta from the Ileum*.—In table 3 the results of the quantitative estimations made on the food, the urine and the dejecta from the ileum are recorded. As has been said previously, each period was three days in length. The intake, which was the same during each day of a given period, is listed in table 1. It will be noted, however, that the intakes for the three periods differed. The results in table 3 are

expressed in grams and are the average daily values obtained from an analysis of a total collection for three days. All analyses were carried out in duplicate. The material recovered from the isolated colon, although of great interest in this study, has not been included in determining the balance (table 3), since the quantities were not large enough to affect the results significantly. Furthermore, no allowance has been made for excretion through the skin.

If one turns first to a consideration of the utilization of the organic constituents of food, it is seen in table 3 that these substances were well digested and absorbed after they passed through the stomach and small intestine. Thus, in period 1, when the intake was 10.28 Gm of nitrogen, 121 Gm of fat and 142 Gm of carbohydrate daily, the dejecta from the ileum contained only 1.37 Gm of nitrogen, 8 Gm of fat and 6.7 Gm of carbohydrate during each day. The same relative results were obtained in periods 2 and 3, although the quantities were different.

TABLE 4—*Daily Averages for Dejecta from the Ileostomy Stoma*

	Total Weight, Gm	Water, Gm	Per centage of Water	Sol- idum, Gm	Sodium Concentration Expressed in Water of Ileal Dejecta, Milli- equivalents per Liter	Dry Sub- stance, Gm	Per- centage of Dry Sub- stance	Total Potas- sium, Gm	Potas- sium per 100 Gm of Dry Sub- stance
Period 1	334.4	305	91.3	0.97	138	29.4	8.3	0.122	0.42
Period 2	362.9	341	93.9	1.03	131	21.9	6.0	0.103	0.47
Period 3	455.1	393	86.4	1.32	146	42.1	13.6	0.170	0.40
Daily average for 9 days	384.1	346	90.5	1.11	139	31.1	9.3	0.132	0.43

When the intake and output for each period are compared, it appears that there was a tendency for a greater output of these substances when the intake was large. These differences were not great and are hardly significant.

Noteworthy among the findings was the considerable amount of water in the feces obtained from the ileostomy. In period 1 there was 305 Gm of water, in period 2, 341 Gm, and in period 3, 393 Gm, in the feces obtained daily from the ileostomy. The material which was passed from the ileum contained from 86.4 to 93.9 per cent of water. In table 4, in which the quantitative estimations are expressed in terms of average daily values, it can be seen that the total weight of the dejecta from the ileum varied from 344.4 to 455.1 Gm in the three periods, the average for the nine days being 384.1 Gm. These amounts are far in excess of the daily excretions of stools by a normal person. Although the average daily excretion of feces may vary according to the type and amount of food eaten, it usually is approximately 100 Gm.<sup>3</sup> Considering

<sup>3</sup> Hawk, P. B., and Bergeim, Olaf. *Practical Physiological Chemistry*, ed 10, Philadelphia, P. Blakiston's Sons & Co., 1931, p. 355.

that the normal stools often consist of 70 per cent water and 30 per cent dry substances, it is of interest to calculate the amount of water which the colon would remove from the ileal dejecta should the continuity of intestinal tract in this case be restored. The average daily excretion from the ileostomy stoma during the nine days was 384.1 Gm., and the amount of dry substance in this excretion was 31.1 Gm. (table 4). On this basis, the amount of water which would be present in a normal stool which contained this amount of dry substance would be 72.6 Gm., and the total weight of this theoretical normal stool would be 103.7 Gm. This is approximately a normal amount. Consequently,

TABLE 5—*Distribution of the Total Daily Output Between Urine and Ileal Dejecta*

Substance	Total Output, Gm	In Urine		In Ileal Dejecta	
		Gm	Total Output, %	Gm	Total Output, %
Period 1					
Phosphorus	0.9720	0.7700	79.2	0.202	20.8
Calcium	0.5610	0.2740	48.8	0.287	51.2
Magnesium	0.1620	0.0650	40.1	0.097	59.9
Potassium	2.4400	2.3200	95.0	0.120	5.0
Sodium	1.9900	1.0200	51.3	0.970	48.7
Chloride	3.5000	2.9300	83.7	0.570	16.3
Iron	0.0078	0.0003	3.6	0.0075	96.4
Period 2					
Phosphorus	0.8250	0.7030	85.2	0.122	14.8
Calcium	0.3660	0.2020	55.2	0.164	44.8
Magnesium	0.1250	0.0610	48.8	0.064	51.2
Potassium	2.0500	1.9500	95.0	0.100	5.0
Sodium	1.5400	0.5100	33.1	1.030	66.9
Chloride	2.8500	2.1100	74.0	0.740	26.0
Iron	0.0568	0.0002	0.3	0.0566	99.7
Period 3					
Phosphorus	0.7240	0.5530	76.4	0.171	23.6
Calcium	0.4100	0.2080	50.7	0.202	49.3
Magnesium	0.1340	0.0570	42.5	0.077	57.5
Potassium	2.0500	1.8800	91.7	0.170	8.3
Sodium	1.4500	0.1320	9.1	1.320	90.9
Chloride	2.6900	1.9600	72.9	0.730	27.1
Iron	0.0612	0.0001	0.1	0.0611	99.9

it is obvious that the excessive weight of the ileal excreta was the result of the considerable amount of water which was present. Removal of this water is a function of the large intestine. One function of the colon, therefore, has been indicated, namely, the absorption of water.

As arresting as was the large amount of water in the material collected from the ileum was the quantity of sodium. In table 3 it is noticeable that the amounts of sodium recovered in the ileal dejecta were great. Table 5, in which the distribution of the total output of sodium in the urine and in the ileal dejecta is recorded, vividly shows the situation in regard to the excretion of sodium. When it is recalled that only 1 or 2 per cent of the total daily output of sodium is normally found in the feces,<sup>4</sup> the presence of from 48.7 to 90.9 per cent of the

<sup>4</sup> Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry. Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 766.

total output of sodium in the ileal material is of great interest. In this case the sodium was eliminated in large part through the gastrointestinal tract, and the urine contained relatively little sodium (table 3). This increase in the fecal excretion of sodium, which has been shown by Holt, Courtney and Fales<sup>5</sup> and by us to obtain in diarrheal disease, will be considered in a subsequent report. In diarrheal disease it may be presumed that there is a decreased absorption of fluids by the colon. The small amounts of sodium which were excreted in the urine (1.02 Gm. in period 1 and 0.13 Gm. in period 3) demonstrate that there is a mechanism which tends to preserve the total base in the bodily fluids. The inorganic constituents of the blood serum of this subject were found to be normal on several occasions, which would be expected in the state of health which she maintained. The results of the analysis of the urine excellently demonstrate the ability of the organism to compensate, at least within limits, for the loss of base through the gastrointestinal tract. The excretion of potassium, however, was not greater in the ileal material than it is in normal feces, only from 5 to 8.3 per cent of the total amount of potassium excreted daily was present in the ileal material. It has been interesting to determine the circumstances attending the output of sodium and potassium in these watery intestinal excreta, in accordance with the suggestion of Peters<sup>6</sup>. In table 4 it may be seen that the excretion of sodium was directly proportional to the output of water in each of the periods of metabolic study, although the amounts of each substance excreted differed from one period to another.

In order to demonstrate the regularity of this finding, the concentration of sodium in the total water of the ileal dejecta has been calculated in milliequivalents per liter (table 4). These concentrations were fairly constant, they ranged from 138 milliequivalents per liter in period 1 to 146 milliequivalents per liter in period 3, the average daily value for the nine days being 139 milliequivalents per liter. On the other hand, the output of potassium was proportional to the total dry substance (table 4). The concentration of potassium in the total dry substance was fairly constant. Although there was an increase in the amount of water and sodium of the ileal dejecta in period 2 over period 1, the amount of potassium decreased, and accompanying this decrease there was less total dry substance in period 2 than in period 1. The distribution of chloride between the urine and the gastro-intestinal excretion also was disturbed (table 5) but to a less extent than was the distribution of sodium. Whereas in normal feces the loss of chloride is insignificant, in this case from 16.3 to 27.1 per cent of the

5 Holt, L. E., Courtney, Angela M., and Fales, Helen L. The Chemical Composition of Diarrheal as Compared with Normal Stools in Infants, *Am. J. Dis. Child.* 9:213-224 (March) 1915.

6 Peters, J. P. The Distribution and Movement of Water and Solutes in the Human Body, *Yale J. Biol. Med.* 5:431-467 (May) 1933.

total output of chloride occurred through the intestinal tract. This loss of chloride occurs also in diarrheal disease, as does the loss of sodium.<sup>5</sup>

A consideration of the amounts of sodium, potassium and chloride which were found in the ileal excreta presents several interesting facts. In the first place, it is apparently a function of the colon to absorb in solution this excess of sodium and chloride and probably a certain amount of other minerals, in order to convert into normal feces the material delivered from the ileum. This represents one of the important functions of the colon—the conservation of the total electrolyte and fluid of the body. But it cannot be said that this is an indispensable function, since in the presence of losses from the gastrointestinal tract there is a marked decrease of the urinary output of these substances and the serum electrolyte still is maintained at a normal level. In the absence of the colon the maintenance of an adequate intake of minerals becomes more important than it is in cases in which the colon is present. Second, it has been shown that in the ileostomy dejecta, which are comparable to a diarrheal stool in many respects, the elimination of sodium is proportional to the excretion of water and that the excretion of potassium is proportional to the output of total solids. Since potassium is the predominant base in the cells of man and because the fecal excretion of potassium varies with the total solids of the excreta, the greater excretion of potassium than of sodium in normal feces probably is the result of the cellular origin of the former rather than of any selective impermeability of the intestinal tract. Peters<sup>6</sup> has suggested such an explanation for the relatively large amount of potassium in normal feces, and it is a reasonable one, if it may be presumed that potassium is the predominant base of bacteria. Steele<sup>7</sup> found that the bacterial content of all types of feces may be as great as 38 per cent of the dry weight, and he said that Strasburger estimated that from a third to a fourth of the dry weight of normal feces was due to bacteria. In addition to bacteria, there is a variable amount of epithelial cells from the lining of the intestine. By reference to table 3 it will be noted that the concentration of sodium expressed in the total water of the dejecta of the small intestine of this patient, which varied from 131 to 146 milliequivalents per liter, is somewhat similar to the concentration of sodium in the blood serum and intestinal fluid. Recently, DeBeer, Johnston and Wilson,<sup>8</sup> who have examined the composition of the secretions obtained at various levels of the intestinal tract of the dog, have found that the concentration of sodium is relatively constant

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7 Steele, J. D. The Method of Determining the Total Amount of the Fecal Bacteria by Weight and Its Clinical Significance, *J. A. M. A.* **49** 647-649 (Aug 24) 1907.

8 DeBeer, E. J., Johnston, C. G., and Wilson, D. W. The Composition of Intestinal Secretions, *J. Biol. Chem.* **108** 113-120 (Jan.) 1935.

in succus entericus from the small and large intestines and that it is similar to the concentration of sodium in blood serum (from 146 to 156 milliequivalents per liter). The chloride in ileal secretions was found by these investigators to be from 73 to 87 milliequivalents per liter. In the present case the concentration of chloride expressed in the total water of the ileal dejecta varied from 52.5 to 55.4 milliequivalents per liter. While the values for sodium obtained by DeBeer, Johnston and Wilson demonstrated the similarity between the amounts of sodium in blood serum and in intestinal fluid, values for the chloride in the intestinal contents are lower than those for the chloride in the blood serum. The acid component of intestinal fluid at the ileum is made up in large part by bicarbonate,<sup>8</sup> a fact which explains why the relative loss of chloride is less than that of sodium in the watery excretion of the ileum in the present study.

Whether this expression of the sodium in the water of the ileal dejecta represents the condition that obtains was investigated during controlled periods subsequent to the completion of the study. Collections of fresh excreta from the ileostomy stoma were secured and centrifuged at high speed, and the clear supernatant liquid was decanted and filtered. The concentration of sodium in this fluid was found to be 132.8 and 123.3 milliequivalents per liter, respectively, on two different occasions. The concentration of potassium in these same specimens of supernatant fluid was 4.5 and 4.8 milliequivalents per liter, respectively. The concentration of chloride in these same specimens was found to be 79.7 and 84.5 milliequivalents per liter, respectively.

These considerations give the impression that during the process of alimentation the ileum delivers to the colon its solids and a variable amount of fluid which is probably near osmotic equilibrium with the blood. This fluid and its soluble constituents are then in large part absorbed by the colon.

The distribution of the excretion of the other inorganic constituents (magnesium, phosphorus and calcium) between urine and feces is not remarkable, as there was no demonstrable deviation from the normal, except possibly in the case of calcium, the urinary output of which was somewhat larger than usual (table 5). The variability of the excretion of calcium in the urine of normal persons is well known and depends on several factors, which have been pointed out by Bauer, Albright and Aub.<sup>9</sup>

*Material Recovered from the Isolated Colon*—The results of the analyses of the material which had accumulated in the isolated colon during these metabolic periods are recorded in table 6 A. The amounts

9 Bauer, W., Albright, F., and Aub, J. G. Studies of Calcium and Phosphorus Metabolism. Calcium Excretion of Normal Individuals on Low Calcium Diet, Also Data on Case of Pregnancy, *J. Clin. Investigation* 7: 75-96 (April) 1929.

of substances recorded for period 1 were secured at the end of period 1 of the metabolic study Under the heading period 2 are tabulated the amounts recovered during periods 2 and 3 of the metabolic study Obviously, these weights, when calculated in terms of daily values, would not add a significant amount to the total output and do not materially affect the balance, as has been mentioned previously in connection with a description of table 3 The striking gross finding is that a small amount of any substance was recovered during the first three days and the second six days The amounts of total nitrogen and chloride were small A relatively large amount of potassium was recovered during both periods This again suggests the cellular origin of this base in feces In the

TABLE 6—*Analysis of Material Recovered from the Isolated Colon*

A During Metabolic Study		
	Period 1 Three Day Total, Gm	Period 2 Six Day Total, Gm
Nitrogen	0 11100	0 1330
Chloride	0 04800	0 1980
Sodium	0 02700	0 1330
Potassium	0 10600	0 1980
Calcium	0 01500	0 0130
Phosphorus	0 01600	0 0180
Magnesium	0 00200	0 0020
Iron	0 00053	0 0013

B During a Two Week Uncontrolled Period	
	Fourteen Day Total, Gm
Weight of total substance	65 0000
Dry weight	4 3700
Nitrogen	1 4000
Chloride	0 1190
Calcium	0 0350
Sodium	0 0420
Potassium	0 4030
Magnesium	0 0050
Phosphorus	0 0350
Iron	0 0009

second period (six days) the amount of sodium was relatively large Of particular note were the amounts of calcium and iron which were recovered During the first three days a total of 15 mg of calcium and approximately 0.5 mg of iron was obtained from the isolated colon These amounts, were they to be expressed in amounts recovered daily, would be small, indeed From the results of these analyses of colonic material it appears that either the colon has no special function that is related to the excretion of these minerals or the method which has been used, namely, the diversion of the intestinal stream, has altered its ability in this regard The latter would be a change, however, that would not be expected if the colon possessed a specific excretory mechanism In this study, in which ample time was allowed for large quantities of calcium and iron to collect in the colon should this portion of the intestine be the particular site for their elimination, it has been found that no such condition obtains The quantities of each substance are not large enough

to warrant the assigning of any specific function of the colon in their excretion. Comparing, in period 1, a recovery of 5 mg of calcium with a total output of 561 mg of calcium daily indicates the minor importance of the large intestine as an excretory organ (table 3). Likewise, in the case of iron approximately 0.5 mg was recovered in three days in period 1, yet 23.4 mg was excreted in the urine and feces during the same time. During the following six days approximately 1 mg of iron was recovered during the entire time, yet the intake was approximately 70 mg of iron daily, largely in the inorganic form (see table 3). During the time of the feeding of additional iron (periods 2 and 3) a large amount was recovered from the ileostomy dejecta. The amount of iron in the urine was not increased by this added intake of iron, the daily amount being only 0.2 mg for period 2 and 0.1 mg for period 3. Gottlieb in 1890<sup>10</sup> demonstrated that the amount of iron in the urine is small and that it is not increased by the feeding of large amounts of iron.

As our patient had discharges of material from the rectum every two or three days which simulated normal bowel movements, it was felt that analysis of this material passed from the rectum without the aid of enemas would furnish additional information, particularly since this method would obviate the use of a possibly disturbing factor. Accordingly, the dejecta were collected for two weeks when the subject was not under controlled conditions of intake but on a normal regimen, except for the addition of 60 mg of iron daily (in the form of ferrous sulfate) during the first week. The weight of the total dejecta from the isolated colon during these two weeks was 65 Gm. Analysis of the dejecta is recorded in table 6 B. It is again apparent from the results obtained in the analysis of the excretory product of this isolated colon that the large intestine under these conditions possesses no special function in excretion. The total amount of calcium excreted from the isolated colon in fourteen days was only 35 mg, and the amount of iron was only 0.9 mg.

#### COMMENT

*The Dejecta from the Ileum*—The results obtained in this study have shown that the protein (as indicated by nitrogen values), fat and carbohydrate are well absorbed in their passage through the stomach and small intestine. The amounts of nitrogen, fat and carbohydrate (table 3) found in the ileal dejecta are similar to the quantities of these substances usually found in normal stools.<sup>11</sup>

10 Gottlieb, R. Beiträge zur Kenntnis der Eisenausscheidung durch den Harn, Arch f exper Path u Pharmacol 26 139-146, 1890.

11 Taylor, A. E. Digestion and Metabolism. The Physiological and Pathological Chemistry of Nutrition, Philadelphia, Lea & Febiger, 1912, pp 212 and 215.



There is a general indication in the literature<sup>12</sup> that the digestion and absorption of the various organic portions of the food is completed before the food reaches the large intestine, as the results in this study also have shown

In the case of the inorganic constituents of the ileostomy dejecta no comparable studies have been found with which the results obtained may be compared. The amounts of calcium, magnesium, phosphorus and iron excreted from the ileum would not be unusual in normal feces under similar conditions of intake. Such a situation does not obtain in the case of the excretion of sodium and chloride, however. The most significant findings in the examination of the dejecta from the ileostomy stoma were the large amount of sodium and chloride delivered to the colon for absorption and the indication that this sodium is present largely in the fluid portion of the ileal excretion and that the fluid component of the total material at the ileum is probably in osmotic equilibrium with the blood. The low concentration of potassium in the fluid portion of the ileal excretion in the presence of a fairly large total amount of potassium has intimated some reason for the relatively large amount of this mineral in normal stools and has formed the basis for additional work on this subject.

*Material Recovered from the Isolated Colon*—As the results obtained in this present study indicate that the colon has no specific function in excretion, it has been of interest to review the works usually cited as evidence to the contrary. Calcium and iron are the two minerals almost universally considered to be excreted by the large intestine, and they will be considered in detail.

*The Excretion of Calcium by the Colon*—There is no doubt that calcium is lost from the body through the feces. The early studies on starving men by Lehmann and Friedrich Mueller and their colleagues<sup>13</sup> demonstrated this fact, and numerous workers since have shown that feces normally contain calcium and that the larger loss of calcium usually occurs through the feces rather than through the urine. Donald Hunter,<sup>14</sup> in his review of the metabolism of calcium and phosphorus,

12 Canavero, M. Studio dell'assorbimento dei grassi e delle sostanze proteiche dopo la colectomia (ricerche sperimentali), Policlínico (sez. chir.) **40** 629-641 (Nov.) 1933. Heile, B. Experimentelle Beobachtungen über die Resorption im Dünn- und Dickdarm, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **14** 474-486, 1905. Landt, H., and Daum, K. Physical Characteristics of Residues from the Small Intestine, Arch. Int. Med. **52** 96-104 (July) 1933.

13 Lehmann, Curt, Mueller, Friedrich, Munk, Immanuel, Senator, H., and Zuntz, N. Untersuchungen an zwei hungernden Menschen, Virchows Arch. f. path. Anat. (suppl.) **131** 107, 1893.

14 Hunter, Donald. Critical Review. The Metabolism of Calcium and Phosphorus and the Parathyroids in Health and Disease, Quart. J. Med. **24** 393-446 (April) 1931.

said that it is generally accepted that calcium is eliminated by the large intestine and to a less extent by the kidneys. Various investigators have studied the subject of calcium excretion by the large intestine, and their work represents the basis for the statements that the colon is a more important site for the elimination of this mineral from the body than is the small intestine. Walsh and Ivy<sup>15</sup> have determined the calcium content of various loops of the small and large intestine in dogs and have concluded that calcium is eliminated to a much greater extent by the mucosa of the large intestine than by the mucosa of the small intestine. In their experiments, by using distilled water as an irrigating fluid to recover calcium from surgically isolated loops of intestine, they recovered more calcium from the colon than they did from portions of the small intestine. Stewart and Percival,<sup>16</sup> who used cats in somewhat similar experiments, have concluded that there is a specific mechanism in the colon for the excretion of calcium and that the large intestine provides the main excretory route for this mineral. Taylor and Fine,<sup>17</sup> who used physiologic solution of sodium chloride for irrigation because they found that distilled water irritated the intestinal mucosa, obtained much less calcium from the colon than did the previous investigators. This suggests that an important difference in the results occurs when the irrigating fluid is isotonic.

A possible objection to the method used in these experiments, which depended on irrigation of an intestinal loop with distilled water at more or less frequent intervals, is that this water may accomplish more than its purpose intends. Not only may the minerals secreted into the lumen be washed out, but a certain amount of electrolyte also may diffuse from the intestinal wall into the distilled water. An attempt to establish an equilibrium, one of the steps preceding absorption, may be initiated. In this instance, the length of time that water is permitted to rest in the lumen of the intestine and the number of irrigations given in a stated time become factors. Furthermore, it seems that the dimensions of the surface area of mucous membrane irrigated in each of the segments of intestine is an important consideration if comparisons are to be made of a differentiating nature. In the present study a lapse of three and of six days was allowed for the products which originate in the colon to accumulate, in order to avoid these possible effects of frequent washing. To test the validity of the contention that frequent

15 Walsh, E. L., and Ivy, A. C. Calcium Excretion by the Alimentary Tract, *Proc. Soc. Exper. Biol. & Med.* **25** 839-840, 1928.

16 Stewart, C. P., and Percival, G. H. Studies on Calcium Metabolism. I. The Action of the Parathyroid Hormone on the Calcium Content of the Serum and on the Absorption and Excretion of Calcium, *Biochem. J.* **21** 301-313, 1927.

17 Taylor, N. B., and Fine, A. The Excretion of Calcium Through the Intestine, *Am. J. Physiol.* **93** 544-553 (June) 1930.

irrigation of the colon results in the recovery of a large amount of calcium, four enemas of distilled water were given to the subject within a period of two hours after a preliminary cleansing. The filtrable portion of the returns from the enemas contained 22 mg of calcium (more than was recovered in three days during the study), which indicates the importance of a factor which may have influenced the results obtained by other investigators.

It has been stated that the largest elimination of calcium from the body occurs through the gastro-intestinal tract. The amounts in feces, which represent the excreted portion and the unabsorbed component, cannot be satisfactorily evaluated. It seems that the mechanism by which calcium is excreted in the gastro-intestinal tract might depend on the relative insolubility of its salts, just as does the difficulty of its absorption. Opportunities for the excretion of calcium seem to be greatest in the small intestine, where the extensive chemical changes are proceeding and where great changes in the electrolytes and fluids are in progress. The large amount of intestinal juices poured into the lumen of the small intestine probably contributes in large part to the formation of this insoluble calcium. Calcium will tend to be precipitated particularly in the lower part of the small intestine where the medium is more alkaline.<sup>18</sup> This precipitation of calcium from the intestinal fluid could occur also in the colon, since a considerable amount of calcium is delivered to it from the small intestine. The amount of calcium actually added to the material in the lumen of the colon from the body fluids is expected to be small, when one considers that the fluid delivered to the colon is probably near equilibrium with the blood and that little diffusion of calcium from the latter would be expected. Furthermore, the colon does not produce an important amount of succus entericus, which could be a source of the addition of some calcium to feces.

Heupke,<sup>19</sup> in summarizing his study of the excretory products of the isolated colon in the dog, concluded that the rôle of the large intestine in excretion is minor, and he stated that he believed that the largest part of the mineral constituents of the feces, as far as they are not the unabsorbed residue of food, are excreted in the small intestine.

*The Excretion of Iron by the Colon*—Robschert-Robbins<sup>20</sup> has stated the present day conception of the absorption and excretion of iron, which is that this substance is absorbed in the entire gastro-intestinal tract, although the duodenum and some of the upper portion

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18 Mann, F. C., and Bollmann, J. L. The Reaction of the Content of the Gastro-Intestinal Tract, *J. A. M. A.* **95** 1722-1724 (Dec. 6) 1930.

19 Heupke, W. Ueber die Sekretion und Excretion des Dickdarmes, *Ztschr. f. d. ges. exper. Med.* **75** 83-125, 1931.

20 Robschert-Robbins, F. S. The Regeneration of Hemoglobin and Erythrocytes, *Physiol. Rev.* **9** 666-709 (Oct.) 1929.

of the gastro-intestinal tract play the major rôle. Excretion likewise is largely by the intestinal route, the colon being its site for the great part. Early work on animals by Bidder and Schmidt<sup>21</sup> demonstrated that the greater part of the excretion of iron occurs in the feces. Lehmann and Friedrich Mueller and their colleagues in a study of fasting men, in 1893, demonstrated a daily excretion of 7 and 8 mg of iron, respectively, in the cases of Cetti and Breithaup. Gottlieb<sup>22</sup> showed that 70 per cent of the iron administered subcutaneously to dogs could be recovered in the feces. A great deal of investigation on the excretion of iron was carried out in the last half of the nineteenth century by German workers. Certain studies, notably those of Hochhaus and Quincke,<sup>23</sup> ascribed the greatest rôle in excretion of iron to the large intestine. As early as 1906, however, Meyer<sup>24</sup> critically reviewed the literature on this subject and, in evaluating it, was unable to find that the site of the excretion of iron in the intestine had been determined. Meyer, however, was impressed by the work of Kobert and Koch,<sup>25</sup> who studied the excretory products of a large segment of isolated colon of a human subject. Kobert and Koch recovered only about 1 mg of iron daily from the colon. The experiments of Chevalier<sup>26</sup> in 1914 indicated that the small intestine is the more important site of excretion of iron. M'Gowan<sup>27</sup> has recently reviewed this subject of the movements of iron in the body, and his experimental work with the fowl has shown that the process of excretion of iron is more intense in the duodenum than elsewhere and that it becomes progressively less marked throughout the rest of the intestinal tract.

#### SUMMARY

In this study of a human subject with an ileostomy stoma and an isolated colon the material which was excreted from the ileum was examined in order to determine the composition of the intestinal material delivered to the large intestine. At the same time the substances which

21 Bidder, F., and Schmidt, C. *Die Verdauungssäfte und der Stoffwechsel. Eine physiologisch-chemische Untersuchung*, Leipzig, G. A. Reyher, 1852.

22 Gottlieb, R. *Ueber die Ausscheidungsverhältnisse des Eisens*, *Ztschr f physiol Chem* **15** 371-386, 1891.

23 Hochhaus, H., and Quincke, H. *Ueber Eisen-Resorption und Ausscheidung im Darmkanal*, *Arch f exper Path u Pharmakol* **37** 159-182, 1896.

24 Meyer, Erich. *Ueber die Resorption und Ausscheidung des Eisens*, *Ergebn d Physiol* **5** 698-745, 1906.

25 Kobert, R., and Koch, W. *Einiges über die Functionen des menschlichen Dickdarmes*, *Deutsche med Wchnschr* **47**:883-886 (Nov 22) 1894.

26 Chevalier, Paul. *Recherches sur l'élimination intestinale du fer*, *Arch de med expér et d'anat path* **26** 277-305 (May) 1914.

27 M'Gowan, J. P. *The Absorption and Excretion of Iron by the Intestines and the Nutritional and Therapeutic Value of Its Salts*, Edinburgh *M J* **37**. 85-96 (Feb) 1930.

accumulated in the isolated colon during known metabolic periods were determined in order to estimate the importance of this section of the intestinal tract in excretion

The data obtained have demonstrated that the organic constituents of the food are digested and absorbed before they reach the colon and that the ileum delivers to the colon solid material and a variable amount of fluid which seems to be near osmotic equilibrium with the blood. This ileal material contains a large amount of sodium and chloride when compared with normal feces. A function of the colon in the absorption of electrolyte and water has been indicated.

It appears that the human colon has no specific function in the excretion of minerals. Particularly has it been indicated that no substantial amounts of calcium or iron were recovered from the isolated colon.

The suggestion is offered that it is probable that variable amounts of cellular debris and bacteria may be added to the intestinal contents in the colon, thus augmenting the total mass which ultimately becomes feces. Such a possibility, however, hardly falls into the category of a specific function.

# Progress in Internal Medicine

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## REVIEW OF NEUROLOGY AND PSYCHIATRY FOR 1935-1936

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BOSTON

### HEREDITY

The inheritance of nervous diseases has long been a question which has attracted interest. The fear of inheriting epilepsy or insanity still haunts many persons unnecessarily. Fortunately, scientific investigation is beginning to clarify the problem, and recent political events, such as the Nazi drive for "race purity," have made the problem a timely issue. Since May 1934 a committee of the American Neurological Association has been at work evaluating available data, and a preliminary report on sterilization has been made to the association. The chairman, Dr. Abraham Myerson, has had wide experience in this field and has been assisted by a professional geneticist, Dr. Keeler, and three neurologists, Drs. Ayer, Putnam and Alexander. The report<sup>1</sup> makes a pamphlet of one hundred and thirty-two pages and is full of important data, references and good sense.

Of course there is no doubt about the inheritance of certain neurologic disorders, such as Huntington's chorea, Friedreich's ataxia, hypertrophic neuritis, Leber's atrophy of the optic nerve, atrophy of the peroneal muscles, the muscular dystrophies and paroxysmal paralysis.

In many of these both the lesion and the type of inheritance are well known. But when the discussion turns to such doubtful entities as feeble-mindedness, epilepsy and schizophrenia, the situation is quite different. The especial stumbling block has been a vague, undefined concept known as neuropathic inheritance or degeneracy. All manner of mental diseases and neurologic disorders and all psychoses, including feeble-mindedness, epilepsy and crime, are thus labeled. Up to the present day this doctrine prevails in most of the studies made on the heredity of mental disease, and until lately, under a new guise in the mendelian work it has been given the sanction of the foremost writers. In the excessive development given this theory, headache in an ancestor was given a hereditary value in relation to the mental disease of his descendants. Fainting spells even in a cousin had a dread significance.

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1 Report of the Committee for the Investigation of Sterilization, American Neurological Association, Boston, 1935

and the early writers laid great stress on tuberculosis, cancer, hemiplegia, gout, "rheumatism" and every chronic or semichronic ailment. In other words, any ill that relatives have suffered from that might be called "nervous" has been considered significant. This adding up of unlike traits, of varied polymorphic characters, is about as scientific as the old ornithologic grouping of the birds as "those principally black in color," those "with conspicuous blue plumage" and so forth. The science of genetics, with its new understanding of unit characters, shows that all problems of inheritance need careful analysis, with a meticulous definition of the terms. "While a certain possible trend toward polymorphism may be found and while it is possible that the constitution in which, for instance, epilepsy develops has some relationship to the constitution in which dementia praecox develops, the relationship is not close enough to warrant belief in a general unitary trait back of all psychoses, feeble-mindedness, epilepsy and the like. Consequently a great deal of the work which has been done is entirely invalid and has only historical significance." This is the conclusion reached by Genil-Perrin in an exhaustive study of the history and the effect of the theory of mental degeneration, which deserves a wider recognition than it has received.

One of the commonest medical misconceptions current among the general population and even among physicians is that epilepsy is an inherited disease leading to mental deterioration. In the first place, the word epilepsy merely signifies that the victim suffers from recurrent seizures. These fits may be caused by any one of fifty or more pathologic conditions, and by far the larger number of these conditions are acquired and therefore not inheritable. Probably the greatest cause of epilepsy is cerebral trauma (at birth or later), closely followed in importance by infections of the brain and meninges in infancy and youth. It is obvious, therefore, that if a young sufferer from convulsions asks a physician if he or she may marry, the physician must look up the individual case and if possible determine the etiology of the convulsions before having the slightest scientific right to answer the patient's important query. Of course, there are families in which fits appear as an inherited character, but these are relatively rare. Taking a group of 1,000 patients with epilepsy, Stein<sup>2</sup> found that they had 6,572 parents, siblings and children. Of these, 37 per cent had fits, while in a control group only 13 per cent gave such a history. Fits occurred in 23 per cent of the fathers of epileptic patients and in 35 per cent of the mothers, while in the fathers or mothers of the controls the rate was approximately the same as that for the general population (0.35 per cent). In general, then, it may be said that seizures do

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2 Stein, C. *Am J Psychiat* 12:989, 1933

occur about four times as often in all or any relatives of epileptic patients as in control groups. But even this low figure is an average, and in dealing with an individual patient this means nothing. An epileptic patient belongs either to the large group whose inheritance is perfectly good or to the small group whose inheritance is distinctly bad and should preclude marriage, this can be determined only by a careful investigation of the family tree. There is, however, an exception to this clear statement, i e., even among the patients in whom epilepsy is known to be due to trauma, there is a somewhat more definite family incidence of fits than in a control group<sup>3</sup>. In other words, certain families are more likely to react to cerebral lesions by exhibiting epileptiform seizures than are other families, which might react with headache or with dyspepsia. Only in this limited way can the theory of neuropathic inheritance be reasonably invoked.

The outstanding defect in all the discussion on feeble-mindedness and its heredity has been the tendency to lump all types of feeble-mindedness together and to discuss feeble-mindedness as if it were a unit. A preliminary consideration of the subject matter shows that the cases of feeble-mindedness may be divided into several main groups: (1) those in which the condition is due to sporadic cretinism, (2) those in which it is due to mongolian imbecility, (3) those in which it can fairly well be traced to injury to the brain at birth or to infectious disease shortly after birth, (4) those of so-called syphilitic feeble-mindedness, (5) those in which the condition is due to microcephalus and hydrocephalus, (6) those in which it is due to amaurotic idiocy and (7) the vast mass of cases of feeble-mindedness in which no definite lesions are found and which become known only as a lowered mentality becomes manifest. It is in this unclassified group that one finds the families whose members are feeble-minded. From whatever angle feeble-mindedness is approached, if one excludes cretinism, mongolism and other differentiated types of feeble-mindedness, the results of the various studies show a larger proportion of inheritance of feeble-mindedness than could be expected by any law of chance, in other words, in a considerable segment of feeble-mindedness heredity plays a rôle of importance. It does not appear in the more careful studies that mental diseases and epilepsy are fundamentally related to feeble-mindedness in a biologic sense. Furthermore, authors on the whole agree that feeble-mindedness when hereditary cannot be considered as a simple mendelian recessive character and that if there is a mendelian inheritance it is multifactorial which means, on the whole, that it is practically impossible to predict the results of sterilization of the feeble-minded.

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<sup>3</sup> Lennox, W. G., in *Nelson Loose-Leaf Living Medicine*, New York, Thomas Nelson & Sons, 1933, vol. 6, chap. 31.



It is curious to note that, while the literature is unanimous as to the hereditary character of manic-depressive psychosis, little valuable statistical material is available. Many authors present only charts of selected and particularly highly tainted families. The character is generally considered to be dominant. However, it must be stated that the figure obtained lags behind that which one would expect, and the term irregular dominance might fit the biologic situation better. In a recent paper Rudin states as his conclusion that the incidence of manic-depressive psychosis is twenty-five times as high among the siblings of manic-depressive patients as in the average population. The most recent German study on the subject is that of Luxenburger. He gives about the same figures as Rudin and Hoffmann, namely, a probability for the development of the disease in 32 per cent of the children of manic-depressive parents. Where practical eugenics is concerned, however, Luxenburger advises great precaution and points to the fact that from the marriages of manic-depressive couples children may emerge who do not have the genotype for manic-depressive insanity but present only partial characters of it, which may be of great positive social and eugenic value. He emphasizes the principle of *Nicht schaden!* (do no damage) and advises a strongly individual consideration in every case. Luxenburger himself points to the fact that manic-depressive subjects as a group are socially productive and successful. He demonstrates clearly that in the families of manic-depressive subjects there are about four times as many members of the higher social strata as in the average population (23.3 per cent 87 per cent). It is safe to say that manic-depressive psychosis is inheritable and that whether in mild or severe form it becomes manifest in many of the descendants of those who have the disease.

Rosanoff and his associates<sup>4</sup> have brought additional evidence, through the study of identical twins, that manic-depressive psychosis is the most hereditary of the commoner mental diseases. In a series of twenty-three pairs of monozygotic twins both had manic-depressive psychosis in sixteen instances and only one of a pair in seven instances. A series of sixty-seven pairs of dizygotic twins showed both affected by this psychosis in eleven cases and only one affected in fifty-six instances. In other words, 70 per cent of the monozygotic and 16 per cent of the dizygotic pairs were both affected.

#### SCHIZOPHRENIA (DEMENTIA PRACOX, PARERGASIA)

During the year 1935 two hundred and twenty-nine papers and two books were published on schizophrenia. This fact is noted in order to give an idea of the mass of research that is being directed toward

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<sup>4</sup> Rosanoff, A. J., Handy, L. M., and Plesset, I. R. *Am J Psychiat* 91: 725, 1935.

the elucidation of one of the most difficult problems in medicine, a problem which economically ranks ahead of tuberculosis and cancer when the situation is envisaged in units of days spent in a hospital. In his chapter on the social significance of psychiatry, White<sup>5</sup> shows that in 1933 there were a total of 296,000,000 so-called hospital days in the United States. Of these, 146,000,000 were used by "mental" patients (exclusive of the epileptic and feeble-minded). From the general run of the diagnoses in hospitals for patients with mental disorders one knows that about half the "insane" are suffering from schizophrenia (with the aforementioned exclusions), necessitating a total of approximately 73,000,000 hospital days, which approaches the total for all general diseases combined (85,000,000) and is more than three times as great as that for tuberculosis (22,000,000).

Having stated how prevalent schizophrenia is, one's next duty is to define it. This is difficult because of its many manifestations and because patients with marked schizophrenic symptoms often show some disturbances usually attributed to other diseases. In a practical classification based on personality Meyer<sup>6</sup> describes the disease as one in which there is a personality disorder mainly in the content of thought. There is fixation on topics, with false systematization of ideas, thinking is along lines not acceptable to the average intelligent member of the patient's social group. This is in contrast to the disorders of mood, in which the personality is dominated for long periods by moods of sadness or elation.

Kretschmer considers the problem from the point of view of types of character and says that persons with schizoid characteristics are classifiable into three groups: (1) unsociable and eccentric persons who are devoid of humor, (2) timid, sensitive, excitable lovers of books and (3) docile, stupid persons. "As the cycloid temperament lies between the poles of gaiety and sadness so does the schizoid lie between those of instability and dullness." Bleuler speaks of schizophrenia as a physical illness with a prolonged course, having a superstructure of psychogenic origin determined by the patient's experiences. The thought processes of the schizophrenic patient are characterized by logically unrelated ideas that are related in the patient's mind, a condensation of ideas, unusual symbolization, vagueness and alliteration. These lead to delusions, hallucinations, negativism, stereotyped behavior and catatonia.

In cases of definite schizophrenia some of the signs and symptoms commonly observed are fever, fatigue, headache, cyanosis of the extrem-

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5 White, W. A. *Twentieth Century Psychiatry*, New York, W. W. Norton & Company, Inc., 1936.

6 Meyer, A., quoted by Muncie, W., and White, P. *The Mood-Content Problem and Thymonic Reactions*, Arch. Neurol. & Psychiat., to be published.

ities, low blood pressure, low basal metabolic rate, pupillary disturbances vasomotor disorders and convulsions. It is useless to argue as to which is primary—the physical or the mental. Biochemical and structural changes are active components in any disorder.

This is all ably discussed and summarized in a book by Lewis,<sup>7</sup> just issued by the Northern Masonic Jurisdiction of the Scottish Rite. The author carefully reviews a vast literature and summarizes the trends, giving excellent bibliographies. The clinical features are discussed at length. Under the heading *psychologic* Freud's concept is emphasized—that one must consider three categories of factors: (1) heredity, the sum total of the constitutional equipment of the subject, (2) disposition, due to early environmental influences, and (3) immediate environment. In psychoanalytic idiom, the narcissistic features are of the most interest psychologically. The patient becomes so interested in contemplating himself that he withdraws his interest from the outside world and regresses, sometimes to stupor. Patients who have gone through such stupors not infrequently recover, and some regain enough contact with the physician to describe their experiences. Often their extreme preoccupation was due to fantasies concerning their reproductive and eliminative functions—strange ideas about urine, feces, semen and birth often come out in a startling way. No one who listens to these accounts can help being impressed by their similarity to the types of primitive thinking described by Freud. Even if the patient does not talk, his behavior often clearly indicates his preoccupation with the genitals and excreta. Nevertheless the concept of narcissism is too narrow. In many instances the patient's fantasies are not directed toward his own body.

Jung<sup>8</sup> thinks these fantasies may sometimes come from the deepest level of unconsciousness, the level where the history of the human race is inherited in a "collective unconscious," so that similar delusions like similar folk myths, arise in different parts of the world.

Hoffmann<sup>9</sup> is of the opinion that the reaction type of the schizophrenic patient is predetermined in some way. The "logical superstructure" loses its control and position in the thought structure, thus allowing the archaic-primitive type of thinking to come to the foreground and to appear as expressions of psychotic symptoms. Hoffmann points out that the characteristic appearance of the body types, including the pyknic, asthenic and dysplastic, fortifies the impression that the bio-

7 Lewis, N. D. C. *Research in Dementia Praecox*, New York, National Committee for Mental Hygiene, 1936.

8 Jung, C. G. *Modern Man in Search of a Soul*, New York, Harcourt, Brace and Company, Inc., 1934.

9 Hoffmann, H. *Familienpsychosen im schizophrenen Erbkreis*, Berlin, S. Karger, 1926.

chemical integrations differ in these subjects and may well have something to do with determining deeper regressions

Much has been written about the body types since Kretschmer's pioneer work. Lewis summarizes this well. He believes that there is evidence to suggest at least that those subjects with the asthenic (leptosomic) habitus are psychologically of a schizothymic, introverted, idiotropic make-up, with an abstract, analytic, subjective and suppressed mind and a capacity for schizophrenic disorders. They have a shut-in personality and are given to autistic thinking. In some of the athletic types of subjects and in practically all the dysplastic types dementia praecox tends to develop if the subject becomes psychotic. Therefore, physically the patient with dementia praecox usually exhibits the morphology of one of these three types, although there are many mixtures of the morphologic and personality elements which allow for the arrangement of clinical subgrouping. The pyknic type, as described by Kretschmer, constitutes a large group, which contrasts with the asthenic type and is found chiefly in those in whom manic-depressive psychosis develops.

From anatomic studies at the autopsy table and microscopic examination thereafter little has been learned to elucidate the etiology of dementia praecox. Most of the histologic changes described can be explained as secondary and not causative. Lewis believes that general sclerosis of all the gonads and all the endocrine glands is significant. Also he finds a degree of vascular hypoplasia. A more convincing type of lesion is described by Elvidge,<sup>10</sup> who made repeated biopsies of the brains of a series of schizophrenic patients and observed changes in the oligodendroglia which seemed to run somewhat parallel to the symptom picture.

Physiologic observations have been many and varied. Whitehorn's<sup>11</sup> cardiochronographic records are of great interest because they indicate that the psychotic patient, although he may show superficial signs of emotion, may not show any significant change in the heart rate, whereas a psychoneurotic patient will have a great change of heart rate with emotion but may show little or no outward signs of this. The normal control group lay between these two extremes. In other words, schizophrenia and neurosis are unlike ways of reacting. The neurotic patient seems to overreact with his autonomic system, while the psychotic patient seems to have lost his ability to react adequately with this mechanism. Gildea's<sup>12</sup> work on blood sugar bears out this general

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<sup>10</sup> Elvidge. *Tr Am Neurol A*, to be published.

<sup>11</sup> Whitehorn, J. C., and Richter, H. *The Unsteadiness of the Heart Rate in Psychotic and Neurotic States*, *Arch Neurol & Psychiat*, to be published.

<sup>12</sup> Gildea, E. F., Mailhouse, V. L., and Morris, D. P. *Am J Psychiat* 92: 115, 1935.

idea, for normal subjects in a state of fear show hyperglycemia, while psychotic patients who exhibit all the symptoms of fear may show no change in the blood

Fischer's early work, which showed that many patients with schizophrenia have a low basal metabolic rate and a decrease in the specific dynamic action of protein, has been followed by a great deal of physiologic observations, principally at two centers of research, the Elgin State Hospital, in Illinois, and the Worcester State Hospital, in Massachusetts. At the former Finkelman and Stephens found among other phenomena a low production of heat in response to cold—a dissociation between the appreciation of cold and the defense mechanisms—and no reactive hyperthermia in a group of fifty patients with hebephrenic dementia praecox. They conclude that the disturbance in heat regulation in dementia praecox is probably due to some physiologic condition in the hypothalamus.

Hoskins and his group of investigators<sup>13</sup> found that many schizophrenic patients had a depressed metabolism, but more conspicuous was a tendency to abnormal variability in many bodily functions: urinary constituents, output of urine, blood flow, blood count and blood sugar. The averages of the observations were usually within normal limits, but "nearly all of the functions studied showed a high individual variability." There seems to be a lack of homeostasis.

The results of none of these investigations are particularly striking, but the combined material, so carefully abstracted and put together by Lewis, brings home the conclusion that here in the study of schizophrenia the modern point of view is essential and is bearing fruit. Workers no longer have to waste time over discussions as to whether the disturbance is mental or physical. The soma and the psyche make a working unit. Abnormality in either one may cause disorganization and may precipitate symptoms in a susceptible organism. As Eddington says: "We often think that when we have completed our study of *one* we know all about *two* because *two* is *one and one*, we forget that we have still to make a study of *and*—that is to say of organization."

That certain persons are more susceptible to schizophrenia than others is obvious from the studies on constitution and inheritance, but it seems likely that only those who show extreme involvement, the patients with the worst "stuff" in them, of necessity will later have dementia praecox. Innumerable persons in the community inherit the tendency, are "that sort of person," but with proper hygiene, mental and physical, can live useful and productive lives. Campbell<sup>14</sup> presents the mental

<sup>13</sup> Hoskins, cited by Lewis,<sup>7</sup> chap. 4

<sup>14</sup> Campbell, C. M. *Destiny and Disease in Mental Disorders*, New York, W. W. Norton & Company, Inc., 1935

aspects of the subject in a most convincing way in his Salmon lectures especially in the chapter entitled "Our Kinship with the Schizophrenic"

Therapy is most varied Skolweit<sup>15</sup> discusses various methods that have been tried, ranging from causing a patient to have convulsions by injecting camphor (1) to various glandular treatments—total ovary and insulin being the newest<sup>16</sup> For a disturbed and excited patient a combination of bulbo-capnine and scopolamine seems to work well Psychoanalysis is used with various results in cases in which the symptoms are mild All one can say at present is that each patient must be studied individually from all angles, and then a regimen must be instituted which may give more stability to both the internal and the external environment

#### BLOOD

In the section on schizophrenia some of the changes in the constituents of the blood in relation to behavior have been discussed A great deal of work has been carried on for years along these lines, and little has appeared in the way of tangible results Gildea's observations (previously discussed) are important, in that they indicate that normal subjects show a rise in the sugar content of the blood more easily than psychotic patients Diethelm<sup>17</sup> reports observations by means of the dextrose tolerance test which indicate that anxiety, panic and tension may cause a striking rise in the sugar tolerance curve For example, when at ease a woman with phobias showed the following dextrose tolerance curve

97 (before dextrose)—151, 132, 94 and 86 mg

In a fearful situation three days later the curve was as follows

110 (before dextrose)—165, 153, 86 and 106 mg

Another patient, who was tense and stammered, before being made to telephone and stammer badly showed the following curve

83 (before dextrose)—149, 156, 122 and 77 mg

After acute stammering the curve was as follows

102 (before dextrose)—163, 171, 123 and 98 mg

He discusses twenty-six cases and wisely warns that it is difficult to evaluate critically the emotional factors, for the depth and acuteness of emotional responses cannot be judged by the outward display even of normal subjects

As regards a relationship between the lipid content of the blood serum and the body build, Gildea, Kahn and Man<sup>18</sup> have done an

15 Skolweit, W Fortschr d Neurol, Psychiat 8:256, 1936

16 Benedek, L Insulin-Schock-Wirkung auf die Wahrnehmung, Berlin, S Karger, 1935

17 Diethelm, O Influence of Emotions on Dextrose Tolerance, Arch Neurol & Psychiat 36 342 (Aug) 1936

18 Gildea, E F, Kahn, E, and Man, E B Am J Psychiat 92:1247, 1936

important piece of work. Men in good health were selected from a university community on the basis of their close conformity with one extreme or the other of a bipolar classification of body build. The subjects who corresponded in most respects to Kretschmer's description of the pyknic in physique represented one extreme, and the slender subjects, the leptosomes, the other extreme. It was found that the lipid content of the serum (total fatty acids and cholesterol) was consistently higher in the seventeen men of pyknic body build than in the twenty-four men of leptosomic physique. The difference between the total fatty acid content of the pyknic and that of the leptosomatic subjects was marked, being eight and seven-tenths times as large as the probable error of the difference. A pyknic body build, a high output of energy and high lipid values were considered as pyknophilic factors. A leptosomic body build, a low output of energy and low lipid values were considered leptophilic factors. These findings suggest that a relationship exists among at least three of the morphologic, biochemical and functional factors that make up the person who represents a relatively pure form of either the pyknic or the leptosomic physique.

#### HYPOTHALAMUS

It has been known for many years that lesions in the nuclei about the third ventricle, below the thalamus, cause somnolence in man. It has now been shown that these lesions in animals (cats and monkeys) will do the same. Moreover, stimulation of this part of the brain sets up a complex reaction pattern characteristic of intense emotion: rapid respiration, dilatation of the pupils, erection of hair and constriction of blood vessels. It has been observed also that after the removal of the cerebral hemisphere and thalamus of a cat, leaving the hypothalamus intact, the animal is subject to great fits of rage. If, however, the hypothalamus is injured, this rage reaction is lost. Thus there seems to be a center in the hypothalamic region where emotional reactions are integrated and where vegetative functions are controlled. The nuclei in question are located at the transition of the forebrain into the midbrain. There are ten pairs of nuclei closely related anatomically, the more important of which are the supra-optic, paraventricular, mamillary and tuberomamillary nuclei. Ranson and his co-workers<sup>19</sup> have been doing much careful work along anatomic and physiologic lines, which

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19 (a) Ranson, S. W., Kabat, H., and Magoun, H. W. Autonomic Responses to Electrical Stimulation of Hypothalamus, Preoptic Region and Septum, *Arch Neurol & Psychiat* **33** 467 (March) 1935. (b) Ingram, W. R., Hannet, F. I., and Ranson, S. W. *J Comp Neurol* **55** 333, 1932. (c) Kabat, H., Magoun, H. W., and Ranson, S. W. Electrical Stimulation of Points in the Forebrain and Midbrain. The Resultant Alterations in Blood Pressure, *Arch Neurol & Psychiat* **34** 931 (Nov.) 1935.

has added greatly to the exact knowledge of this important region. Not only have they produced the aforementioned symptoms, but they have found a well localized point in the lateral hypothalamic area stimulation of which causes a rise in blood pressure.

Clinicians have not been backward in taking up the lead, and now a great many syndromes are described as due to hypothalamic lesions. Lhermitte<sup>20</sup> enumerates diabetes insipidus, narcolepsy, hyperorexia, glycosuria, lipodystrophy, retinitis pigmentosa and adiposogenital dystrophy and adds others that are less well substantiated. Obviously much more needs to be learned. So many and so varied functions cannot be controlled in so small an area. The probability is that the hypothalamus is one of several regions where vegetative nuclei are clustered and where integration of vegetative function takes place. All important functions are controlled from several levels of integration.

Bearing on this is the recent work from Fulton's laboratory. Kennard<sup>21</sup> extirpated various parts of the cerebral cortex in monkeys and found that lesions in area 6a of the frontal lobe caused cooling of the contralateral side of the body, a diminution of sweat and sometimes edema. Kabat, Magoun and Ranson<sup>19c</sup> found an area in the frontal lobe of cats electrical stimulation of which caused a fall in blood pressure. Some single clinical cases have been reported which give evidence of a similar nature, but the recent paper by Ellis and Weiss<sup>22</sup> reports a study of thirty-five patients with hemiplegia, all of whom had a greater blood flow in the paralyzed arm than in the normal arm, thirteen showed edema of the affected hand. Three patients came to autopsy and showed lesions affecting cortical cells or fibers but not the hypothalamus. There is accumulating good evidence, therefore, that the autonomic nervous system is far from being merely peripheral and automatic but has controlling centers even in the cerebral cortex.

#### PSYCHONEUROSIS

Ross<sup>23</sup> has just written an important book entitled "Prognosis in the Neuroses." He reports on the results of treatment at the Cassel Hospital for Functional Nervous Disorders, at Penshurst, Kent, since 1920. Before discussing the data he critically evaluates the possible errors and discusses the probable fallacies, coming to his conclusion cautiously and intelligently.

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20 Lhermitte, J. *Rev. neurol.* **1** 809, 1934.

21 Kennard, M. A. *Vasomotor Disturbances Resulting from Cortical Lesions*, *Arch. Neurol. & Psychiat.* **33** 537 (March) 1935.

22 Ellis, L. B., and Weiss, S. *Vasomotor Disturbance and Edema Associated with Cerebral Hemiplegia*, *Arch. Neurol. & Psychiat.* **36** 362 (Aug.) 1936.

23 Ross, T. A. *An Enquiry into Prognosis in the Neuroses*, London, Cambridge University Press, 1936.



Three methods of psychotherapy were employed at the hospital—hypnotism, persuasion and analysis. Hypnotism was used only occasionally. "On the whole it is probable that it affects the prognosis adversely—it does not tend to enable the patient to stand on his own feet. No one who has used it doubts its immediate potency, but that is of little importance." Persuasion connotes not suggestion but a more educational process. A long history is taken that eventually brings up forgotten things, a meticulous examination is carried out, and it is demonstrated to the patient that most of his symptoms commonly accompany emotion in everybody. It is then pointed out that the methods of management of his life in the past were bad. After this, in many instances, the symptoms disappear.

Analysis, as the term is used by Ross, is not the regular Freudian procedure but an eclectic application of psychologic methods for studying each patient individually. "Our belief was largely in an individual psychology, i. e., that the patient's personal experience was the important thing, some of this when he came under observation was conscious, some of it had become unconscious, we were interested also in trends which had not yet become experience, and often not yet conscious. What we aimed at was to discover what experiences an individual had encountered and how they had affected him. Much of this is often repressed, and the exploring of such repressions is frequently, as it seems to me, of more value than following the development of the infantile mind through the various stages which have been described by the Freudians, but which were possibly invented by them."

Besides these forms of therapy there were general medical supervision, contact with other patients with all its educational implications, occupational therapy, work and organized games.

In these ways 1,186 patients were treated between 1920 and 1934. Reports one year after discharge showed 45 per cent well, 25 per cent improved and 19 per cent not benefited. Reports after three years were not quite so good—40 per cent well and 10 per cent improved, but there were many more "lost sight of", after five years 34 per cent were well and 6 per cent were improved, the falling off probably being partly due to losing track of the patients. Special groups are discussed. The obsessional and compulsive neuroses seem to be the most difficult to treat. Concerning traumatic neurosis, he wisely remarks "If the legal profession, bench, bar and solicitors, could grasp the conception of neurosis, and if it were possible that legislators could become capable of being educated to see that not trauma, but advantage to be gained by a history of trauma, was what made these people ill, this form of illness would disappear." Among alcoholic subjects he finds that homosexuality plays a considerable rôle.

Freud's<sup>24</sup> "Autobiography" is another milestone in the psycho-analytic field. The historical sketch of psychoanalysis is one of the best expositions extant of what it really is all about. For instance, in chapter 3 he says "The theory of repression became the foundation-stone of our understanding of the neuroses the task of therapy as to uncover repressions and replace them by acts of of judgment." Again in chapter 4 he says "The theories of resistance and of repression, of the unconscious, of the etiological significance of sexual life and of the importance of infantile experiences—these form the principal constituents of the theoretical structure of psychoanalysis." And "What poets and students of human nature had always asserted turned out to be true the impressions of that remote period of life, though they were for the most part buried in amnesia, left ineradicable traces upon the individual's growth and in particular laid the foundations of any nervous disorder that was to follow. But since these experiences of childhood were always concerned with sexual excitations and the reaction against them, I found myself faced by the fact of infantile sexuality—once again a novelty and a contradiction of one of the strongest of human prejudices." In this last passage crops up again what I have criticized before, the use of such unscientific words as any and always, but in this autobiography one can find the main theories expressed simply and clearly.

In May of this year was celebrated the eightieth birthday of Sigmund Freud. It is interesting that the principal speaker at the Vienna occasion was an artist, Thomas Mann,<sup>25</sup> who explained how much the freudian theory has illuminated literature and explained philosophic concepts like those of Schopenhauer. He feels that psychoanalysis has brought a healthy skepticism into the world "which unmasks all the schemes and subterfuge of our own souls." Freud once called his theory of dreams "a bit of scientific new-found-land won from superstition and mysticism." The address is interesting reading, it shows how widely the freudian doctrines have spread, it is not so much what Thomas Mann says as the fact that he says it!

24 Freud, S. *Autobiography*, translated by J. Strachey, ed. 2, New York, W. W. Norton & Company Inc., 1935.

25 Mann, T. *Life and Letters Today* 15 80, 1936.

## Book Reviews

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**Medical Papers** Dedicated to Henry Asbury Christian, Physician and Teacher  
From his Present and Past Associates and House Officers at the Peter Bent  
Brigham Hospital, Boston, Massachusetts Price, \$10 Pp 1,000 Baltimore  
Waverly Press, 1936

This handsome volume contains no less than a hundred contributions by students and associates, past and present, of Dr Christian, published in celebration of his sixtieth birthday. The reviewer has seen few *Festschriften* more imposing and none which conveys a stronger impression of love and respect on the part of those who have joined in a tribute to their friend and teacher. The reviewer, though not directly associated with Dr Christian, takes this opportunity to add his inarticulate homage to a man who has always stood for the best in American medicine—sound practice, unswerving search for the truth and stimulating guidance of students and associates. Dr Christian has achieved the rare privilege of becoming, like Shattuck, Osler and Thayer, a tradition in his own lifetime. The subjects of the various essays show, as one might expect, a wide range of interests. It is not possible to go into detail here, but almost every phase of internal medicine is touched on. Some of the work comes from the laboratory, and at the other extreme is a pleasant sprinkling of philosophic essays dealing with medical practice and teaching. Finally, the register of the former and the present members of the medical staff of the Peter Bent Brigham Hospital adds a note of biographic interest.

**Traité de physiologie normale et pathologique** Edited by G H Roger  
and L Binet Volume X Physiologie nerveuse (deuxième partie)  
Fascicles 1 and 2 Price, 250 francs Pp 981, with 275 illustrations Paris  
Masson & Cie, 1935

The appearance of this work completes the first volume. Volume IX, which was published in 1933, also dealt with the nervous system.

The work is primarily one of reference for French students of medicine. It reviews in some detail the more important features of physiology, with considerable attention to the historical background. The volumes are far from complete, however, in their presentation and are evidently not intended for the specialist, except in a few instances in which the sections are written by persons preeminent by virtue of important contributions to the subject.

**Elektrokardiographische Befunde bei Herzinfarkt** By Anton Jervell Pp  
267, with 112 illustrations Oslo Kirstes Boktrykkeri, 1935

This book is a reprint of an article in *Acta Medica Scandinavica*, written by Dr Anton Jervell, first assistant in Professor Muller's clinic in Oslo. Electrocardiographic-minded physicians will appreciate it.

In brief, Jervell describes the electrocardiographic findings which he observed in a series of sixty-five patients with coronary thrombosis, thirty-six of whom were followed up to section. The book is attractively arranged, the reports of the cases are short and to the point, and the illustrations, which comprise tracings and diagrams of the heart, are admirably clear. A bibliography of two hundred and seventy-two references to the recent literature on coronary thrombosis concludes the volume. On the whole, this monograph represents excellent workmanship and is an admirable contribution to the subject of cardiovascular disease.

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